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AN INTERNATIONAL FORUM FOR THE ADVANCEMENT OF MEDICAL SCIENCE BY STUDENTS

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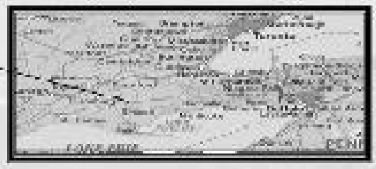

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GRAND RIVER HOSPITAL

First Prize

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MJM 9(2):8-14; 2006

Norzeihan Jan Bappu, Panangipalli Venugopal, Akshay Kumar Bisoi, Pankaj S Mankad

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Second Prize

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MJM 9(1): 8-13; 2006

Chigozie Jesse Uneke, Ogbonnaya Ogbu, Vincent Nwojiji

EDITORIAL

"The problem of neurology is to understand man himself"
Dr. Wilder Penfield

For most of the history of Western medicine, the fields of neurology and psychiatry have been intricately linked (1). Ironically, it was the pioneering psychoanalytical work of Freud, a neurologist, which helped to initiate what became a growing schism between neurology and psychiatry (2). Neurology, focused more on neurobiology, evolved along a parallel yet completely separate line from psychiatry, which took a more biopsychological approach to the understanding of the human brain. While there was much progress in both fields, they continued to grow apart through sub-specialization, in their organizational culture and in their understanding of the human brain. There were those who dared to go against the current and attempted to break down the wall between these two disciplines, but successes were few and far between and those well established in each discipline did not look well upon them. As Dr. Brenda Milner, a pioneer in the field of neuropsychology, recounts in the feature interview of this issue (3), Donald Hebb was among the first to advocate the merging of neurosphysiology with neurospychology despite disapproval from many of his prominent colleagues. Later, Dr. Milner herself had to fight against the prevailing disparaging attitude of the day toward a synthetic approach to the study of neuroscience in order to carry out her work.

Today there is far more agreement that it is not only possible, but necessary to unite the study of anatomy, physiology, and behaviour in neuroscience. More recently, many efforts have been made in the medical community to bring together the fields of psychiatry and neurology. One example is the creation and growth of combined neurology and psychiatry, i.e. neuropsychiatry residency programs in academic centres across North America since the 1980's. Currently, the Fellowship and Residency Electronic Interactive Database lists 10 such combined post-graduate training programs (4). It is reasonable to expect an increase in number of similar programs in North America in the upcoming years, as the programs mature and graduates establish themselves as physician and scientists in the medical field. Although it might still be too soon to judge the success of such initiatives, those hoping for more integration between neurology and psychiatry will certainly agree that a step in the right direction has been taken.

Although integration, or at least discussion, between the disciplines and specialties is an important step, Dr. Milner points out quite rightly that a more difficult task ahead is to integrate our knowledge of the molecular aspects of neuroscience into our understanding of the human brain (3).

Research in the molecular neurosciences has been prolific over recent years. This is encouraging, and may provide a key role in removing the 'wall' that exists between physiologists and behaviourists, or psychiatrists and neurologists. In the past, molecular research was hampered by limitations in technology, making it difficult to either prove one's own hypothesis, or refute another's, thus creating further divisions within the field. Often, evidence for cerebral processes was indirect, or based on inferences found in principles from other fields. One example of this is the field of neuroimmunology. Only twenty years ago, many considered that the central nervous system was isolated and protected from most inflammatory responses, presumably due to the presence of the blood brain barrier (BBB). This theory was logical, but difficult to test at the time. However, as advances in molecular biology, cell culture, and medical imaging progressed, it is now clear that the immune system plays a major role in the pathophysiology of both acute and chronic neurological disorders such as stroke, brain trauma, Alzheimer's Disease, and multiple sclerosis. Research has demonstrated clear relationships between immunology and the CNS, bridging immunologists and neuroscientists, and forming this relatively young field.

Others are venturing further, with the emergence of psychoneuroimmunology (5). The field integrates researchers from several scientific and medical disciplines, including neurosciences, psychology, immunology, physiology, pharmacology, psychiatry, behavioural medicine, infectious diseases, and rheumatology, who are interested in interactions between the nervous and immune systems, and the relationship between behaviour and health. In fact, a recent review by Diamond et al. provides evidence for the role of serum antibodies to the N-methyl D-asparate receptor, which occur frequently in patients with systemic lupus erythematosus, to alterations in cognition and behaviour, following a breach in the BBB. (6) Taken together, neuroimmunology is only one of the many fields of neuroscience whose progress has led to not only a greater understanding of disease, but an understanding shared amongst scientists and clinicians from multiple disciplines.

To summarise, the investigation of the human mind and brain, at once both the same and different, has taken a path thus far reminiscent of many other fields within science and medicine. First, one broad area of

study progresses and advances. It is then forced to sub-specialize and compartmentalise, allowing researchers and clinicians to create for themselves pockets of understanding. Later, further advances in understanding and technology finally allow scientists to begin reintegrating and synthesizing between seemingly disparate fields which actually originated from a common thread. We can look forward to great advances in the future of neuroscience as researchers and clinicians continue to expand upon their understanding of the brain and the mind, and its complex interactions with the body.

How should we prepare for what lies ahead? In his reflections published in this issue, Dr. Colman, the current director of the Montreal Neurological Institute, muses upon the role of serendipity in significant scientific advances, but also upon the importance of broadening horizons and being aware of what is around you as one may see something where another may not (7). Most importantly, perhaps, he also stresses the importance of good preparation as the soil in which serendipitous events may seed and grow. We should remember, as scientists and physicians in training, that good preparation include both a solid understanding of the field of neuroscience, as well as developing a broad set of skills.

As a parting thought, and a playful, yet sobering reminder of our humanity, it is interesting to question how far our understanding of the mind has the potential to go. After all, are there not limitations in using the human mind to study the human mind? How can the brain objectively understand itself fully? These are, perhaps, questions best left to philosophers. At least for now…

REFERENCES

1. Baker MG, Kale R, Menken M. The wall between neurology and psychiatry. BMJ 324(7352):1468-9. Jun 22, 2002.
2. Stone J, Carson A, and Sharpe M. Wall between neurology and psychiatry, some parts of the wall are thicker than others. BMJ 324(7352):1468-9; Jun 22, 2002.
3. Milner B and Xia C. Understanding the human brain: A lifetime of dedicated pursuit. McGill Journal of Medicine 9(2):86-93; 2006.
4. Fellowship and Residency Electronic Interactive Database. http://www.ama-assn.org/ama/pub/category/2997.html. Last accessed July 29, 2006.
5. Prolo P, Chiappelli F, Fiorucci A, Dovio A, Sartori ML, Angeli A. Psychoneuroimmunology: new avenues of research for the twenty-first century. Ann N Y Acad Sci. 966:400-8; June, 2002.
6. Diamond B, Kowal C, Huerta PT, Aranow C, Mackay M, DeGiorgio LA, Lee J, Triantafyllopoulou A, Cohen-Solal J, Volpe BT. Immunity and acquired alterations in cognition and emotion: lessons from SLE. Adv Immunol. 89:289-320; 2006.
7. Colman D. The three princes of Serendip. Notes on a mysterious phenomenon McGill Journal of Medicine 9(2):82-84; 2006.

Sasha Carsen, B. Sc. (Hon.), M.D.C.M. (2008), MBA (2008) and **Chenjie Xia,** M.D.C.M. (2008) are the tenth Editors-in-Chief of the MJM. Sasha's research interests include health policy and management, and he has done research with the Canadian Health Services Research Foundation. Chenjie's current research focuses on cognitive neuroscience, more specifically the roles played by different neural substrates in the regulation of affect. **Christopher Fordyce** (M.D.C.M. 2008) is the Executive Senior Editor of the MJM. He received a B.Sc (Hons) in Life Sciences from Queen's University and an M.Sc. in Physiology and Neuroscience from the University of Toronto. His graduate work in neuroimmunology focused on the role of microglial K+ channels in immune-mediated neurotoxicity.

LETTER TO THE MJM

STUDENT JOURNALS: FACILITATING MEDICAL STUDENT RESEARCH AND PHYSICIAN-SCIENTIST DEVELOPMENT

Dear *MJM*,

There is growing concern over the declining number of physician-scientists over the last two decades. Although James Wyngaarden, former National Institutes of Health Director, called attention to this issue more than 25 years ago (1), history tells his concerns were mostly ignored. The number of physician-scientists decreased by more than 6% from 15,377 in 1980 to 14,434 in 1997. In the same period, there was almost a doubling of physicians reporting patient care as their primary career from 376,512 to 620,472 (2), thus confirming a declining interest among physicians to perform biomedical research as their primary professional activity, which is the general definition of physician-scientists. Physician-scientists generally include those who conduct basic science, disease-oriented, and/or patient-oriented research.

Does it really matter if physicians play a small role in medical research? After all, there is a growing number of competent Ph.D. scientists performing clinical research (2). Dr. Leon E. Rosenberg offered a response, "It may be true that a medical education does not adequately prepare one to answer scientific questions, but it is the ideal setting in which to ask them (3)." Physicians ask questions that reflect their experiences based on direct care of patients. They also act as the link between bench and bedside. Physicians can communicate their work with both scientists and other health professionals more directly than any other group. At the end of his article, Dr. Rosenberg proposed five recommendations that addressed the declining number of physician-scientists, one of which was establishing and maintaining a supportive environment in medical schools, which encourages and rewards students committed to research (3).

Modern medical schools incorporate both scientific method and critical appraisal into their traditional basic science/clinical education. This is important to training future physicians to practice evidence-based medicine (EBM). The future of EBM does not rely solely on learning methodology but includes the active participation of physicians in research. Extracurricular research has long been encouraged in medical schools and is recognized as an important determinant in the decision to continue postgraduate research (4,5). Furthermore, high quality medical student research is publishable in peer-reviewed journals and can contribute considerably to the scholarship of a medical faculty (6,7).

Since 1997, there has been a small but encouraging increase in interest in research as part of their careers among medical students (8). It is important to continue the efforts made to maintain this trend and to support medical students in their endeavours to become physician-scientists. And this is where student journals play a critical role.

Although student journals have long been recognized to offer opportunities for students to express their ideas, the impact of student journals to spark research interests is often understated. Student journals have the unique opportunity to engage students at a more personal and understanding level. They recognize that for many students publishing their first article is a daunting task. Many students can spend numerous hours writing and revising their submissions to leading journals only to have their confidence crushed by a rejection letter. The mandate of student journals is particularly sympathetic to submissions from students who are embarking on their research careers. Even if they have no scientific data to submit an original article, students can make contributions in other forms such as letters and commentaries. Critical appraisal letters can often demonstrate a student's competence in using the scientific method and are likely to stimulate interest in research and academic medicine (9). Many students have published their first articles in student journals. Indeed, student journals, including the McGill Journal of Medicine, have often been the launching pad for those aspiring to research careers.

Many student journals are advocates for high quality medical and scientific research, and devote many of their pages to scientific evidence in the form of original research and review articles. However, it is equally important to maintain a balance in medicine and recognize that not all aspects of medicine lend themselves to rigid study. The art of medicine still involves an exchange of ideas and opinions. Furthermore, many student journals provide eager students the unique opportunity to be part of an editorial board in which to learn and practice their critical appraisal skills. A balanced approach to medical science will enable student journals to encourage critical thought, student research, and willingly, the development of future physician-scientists.

Sincerely,

Steven Lin, BMSc
MD,CM 2007 Candidate
MJM Consultant

REFERENCES

1. Wyngaarden JB. The clinical investigator as an endangered species. N Engl J Med 1979; 23:1254-9.
2. Zemlo TR, Garrison HH, Partridge NC, Ley TJ. The physician-scientist: career issues and challenges at the year 2000. FASEB J 2000; 14:221-30.
3. Rosenberg LE. Physician-Scientists-Endangered and Essential. Science 1999; 283:331-2.
4 Segal S, Lloyd T, Houts PS, Stillman PL, Jungas RL, Greer RB. The association between students' research involvement in medical school and their postgraduate medical activities. Acad Med 1990; 65(8):530-3.
5. Jacobs CD, Cross PC. The value of medical student research: the experience at Stanford University School of Medicine. Med Educ 1995; 29(5):342-6.
6. Wehrens XH, Leiner T. Publications from extracurricular research. Lancet 2001; 358(9284):846.
7 Cursiefen C, Altunbas A. Contribution of medical student research to the Medline-indexed publications of a German medical faculty. Med Educ 1998; 32(4):439-40.
8. Ley TJ, Rosenberg LE. The physician-scientist career pipeline in 2005: build it, and they will come. JAMA 2005; 294(11):1343-51.
9. Hanratty B, Lawlor D. Getting letters published in journals is good aim for medical students. BMJ 1999; 319(7218):1198.

Steven Lin is a MJM Consultant and previous Editor-in-chief. He received his B.M.Sc.(Hon.) in physiology from the University of Western Ontario. His research in cardiovascular disease has earned him scholarships from the Heart and Stroke Foundation and St. Michael's Hospital in Toronto, Canada.

COMMENTARY

Who do I serve?

An address to the class of 2008 at the White Coat Ceremony on October 11th, 2005 in the Faculty of Medicine - McGill University*

Charles Scriver

This talk is inspired by the story of Matthew about whom you will hear in a few moments.

This ceremony acknowledges a transition in your medical education: A rite of passage from the study of basic medical science in classrooms to new encounters with patients at bedsides and in clinics.

On choosing and being chosen

You are an exceptional group of women and men. In the style of praise we have come to know from Lake Woebegone one could say that all the men here are strong, all the women are beautiful, and being the children of your parents, you are, of course, all well above average.

You chose to study medicine I assume it was a matter of free will that led you to this choice, but what was your motivation to make it? Was it to serve your patients, or was it for the prestige of being a doctor, or to be blunt, was it for the money and the lifestyle? Did you have an epiphany of vocational passion and compassion, as described perhaps in your application essay to wherever it was sent, and will that essay make interesting and honest reading 25 years hence? A better question: Who will you serve all your days as a physician and in so doing, will you be true to yourself?

While you made a choice and applied accordingly, you were also chosen. Many were called, but fewer were chosen to become members of the Class of 2008. Some of you may wish to question and evaluate the criteria by which the selection process operates, but having been chosen you are privileged; and as a result, you have acquired responsibilities: to yourself; to your family and friends who helped you to succeed; and also to your mentors -who have expectations of you.

At this stage of your life, you have chosen to acquire a body of knowledge about the illnesses and diseases from which your fellow human beings can suffer; in due course, you too will suffer from one or other of those illnesses and diseases. Therefore, it is fair to say that while they are conditions that undermine our wellbeing, the diseases also reveal the importance of our health. Accordingly, the good physician has two roles: one to diagnose, to explain and to treat disease; the other to listen, to heal the person with the illness, and to bring that person back to a state of health.

Life and now

"Life can only be understood backward but it must be lived forward." The philosopher Kierkegaard, whose aphorism this is, was echoing an enduring theme about life and its trajectory, equally apparent in a little folk rhyme: Yesterday is history, Tomorrow is a mystery; Today is a gift, and we call it - the Present. Whichever version you prefer, it refers to the gift of life in past, present and future terms. You have chosen to serve the present lives of your patients. Your encounters with those lives may primarily involve events around procreation, birth and childhood; or they may be

* The White Coat Ceremony of McGill Faculty of Medicine is entitled "Donning the Healer's Habit" and pays homage to the late Dr. Joseph Wener, a cardiologist, internal medicine specialist, and a popular teacher. Faculty, students and their loved ones are gathered in a ceremony which focuses on the white coats, a symbol of compassion and patient care rather than power. The Ceremony takes place during the second year of the medical students' education at McGill Faculty of Medicine and marks their transition from being in the classroom to being in regular contact with patients. Dr. Charles Scriver was invited to give the keynote address at this Ceremony.

† Dr. Rita Charon, Keynote speaker at the White Coat Ceremony to the class of 2007, spoke about choosing and being chosen to study medicine; her address was titled "Levitation of Care". Her thoughts find echoes here.

encounters contained within the odyssey of an individual's lifespan; or they may be encounters mainly with the ending of a life.

Ever since humankind began to describe and record its view of life, for example in the Sumerian epic Gilgamesh, or in Homer's The Odyssey, we have been told that our mortality (call it death) is what makes life itself so interesting and important. In our profession of medicine, there is a counterpart to that awareness: it is disease and illness that make health so important. But life with disease is suffering, and if, as physicians, we do not address the suffering, we will have ignored the place of healing in our profession. Our medical expertise, no matter how extraordinary it may be, has assisted in only part of the journey back to health. Physicianship is a term that embraces both the fixing of the disease and the healing of the person. We use knowledge about the illness to understand its effect on health; we use compassion and empathy for the process of healing; and when we are complete physicians, we are also aware of the role that culture plays in our views of health and disease.

Poets have ways of saying things that get to the core of a theme. Here is one example - from TS Eliot (1):

Where is the Life we have lost in living?
Where is the Wisdom we have lost in knowledge?
Where is the Knowledge we have lost in information?

It has taken me a fair portion of my lifespan to appreciate the density of the messages in those subtle questions. When I graduated with my MDCM in 1955, I was full of information; I was very proud of it and I was probably arrogant. I know now that I had too little knowledge at the time and very little wisdom. I would have been better prepared as a physician if I had been more humble; the poet again had something to say about that (2).

The only wisdom we can hope to acquire is the wisdom of humility - humility is endless.

Mystery, illness and individuality

Life and its emergent properties, for example the assembly of the fetus in the womb, remain imperfectly known; there is mystery here. It would be well for physicians to recognize that there is mystery because we can then begin to appreciate the hold that disease and illness have on the emotions of our patients; and, if we are honest, on ourselves.

With our medical expertise we will diagnose and treat disease. If we do only that, we may forget that there is a patient who has the disease, and in the forgetting we will dehumanize our practice of medicine, and at the same time, erode the dignity of our patient and of ourself. The disease will become the object of our interest and the patient will only be an appendage. We can do better than that and physicianship will help us to do it better by seeing things differently, for example:

i. It is a person, with an illness, who has come to you for help.
ii. The person with the illness, and the disease in the person, are not equivalent.
iii. Every person (every individual human being) has her or his particular form of any nominal disease or illness.
iv. Good doctors know that each patient is a different person, that medicine is a science of the individual, and that to treat only the disease is to treat the patient as an object.

A famous medical anecdote illustrates these ideas: Coleridge, the poet, has already written his great poems such as Kubla Khan and The Ancient Mariner. He is famous, he is in his mid-20s and he is profoundly addicted to opium. Kubla Khan was composed in an opium dream. His friends notice deterioration in Coleridge's health, they fear for him, and they arrange for him to be seen by Caleb Parry, the great physician in the nearby city of Bath. Coleridge goes, Parry receives, Parry cures Coleridge's opium addiction within the year. When asked how he did it, Parry replies: I did not treat his opium addiction, I treated Mr. Coleridge.

If I were to name the chief concerns I have for you, citizens of the Class of 2008, among them, I would name depersonalizing those you have come to serve. You will be drowning in a sea of information. You will be swimming hard to keep up with evolving facts and technologies, and you will be struggling hard to keep up with practice norms and recurrent accreditation requirements. As a result, you may have too little time to listen to your patients, to let them tell you about their own mystery and worries. Somehow, your education, your personal view of life, your profession, and the society that sets the standards for your professional practices, must allow you the opportunity to practice physicianship. Yet, it is possible to keep body and soul in focus even under the most technocratic conditions. Let me illustrate with the story of Matthew.

Matthew's story

The story is told using terms you will learn in the clinical curriculum that lies ahead. The story is simplified for clarity.

Matthew was born on Feb. 24th, 2005, the second child of older parents. His life in utero was monitored by the full array of modern technologies. Nothing adverse was observed except for mild polyhydramnios. Amniotic membranes ruptured at 36 weeks and premature delivery occurred by cesarean section.

Matthew weighed 3.26 kg, a normal weight for the fetal age. Extrauterine life did not begin well; severe respiratory distress required immediate intubation, and congenital anomalies were recognized. An operation on the first day of life identified a tracheo-oesophageal fistula, segmental tracheomalacia, and atresia of the lower oesophagus. The fistula was repaired and the stomach joined to the existing oesophagus. Matthew survived. Post-operative monitoring confirmed suspicion of a cardiac problem and on the third day of life a second trans-thoracic operation was performed to repair his total anomalous pulmonary venous return and to close a large ventricular septal defect. Again - Matthew survived. Friends of the family were correct in applauding both the effectiveness of the anesthesia that made surgery possible, and the awesome surgical and medical expertise that rescued Matthew; in their lay language - it was "a miracle".

Matthew required assisted airway ventilation for various reasons, and because of his oesophegeal problem, it was not possible to feed him on his mother's breast milk by the normal enteral route. He was fed intravenously by total parenteral nutrition (TPN) - another neonatal technology. He gained weight and showed normal cognitive parameters. It was even possible for the parents to cuddle Matthew occasionally, despite all the tubes, monitors and attached equipment.

By the third week of life, it was impossible to ignore another problem. Matthew had chylothorax, probably due to anomalous flow of lymph, explained by extending the field of congenital anomalies to include the thoracic duct. A drain to the exterior was installed to prevent lung compression; and because of the drain, there was a portal for infection; serious infection occurred. Antibiotics were effective and again Matthew survived. Some of his caregivers began to call him "little cat with all those lives"; others referred to a series of "rebirths". Meanwhile, a large community of friends and family praying for Matthew recognized the Spirit at work.

Matthew's set of congenital anomalies might be explained by a single post-zygotic somatic mutation. There was no evidence for an inherited germ-line mutation or syndrome in this scenario. The parents were counselled accordingly.

The story continues. Matthew had received only TPN for his nutrition. TPN can be a poisoned chalice and some infants harboring unknown susceptibility alleles will develop a particular form of lethal liver damage. Matthew developed hepatic cirrhosis and TPN feedings had to be terminated. In the 5th month of life, a jejunostomy tube was inserted and enteral feeding with his mother's milk initiated by this artificial route, because it was still not safe to feed by mouth. All was well, until the bowel perforated, perhaps because its structural integrity had been compromised early by the failure in utero to ingest amniotic fluid and thus condition the bowel. A reaction to the perforation set in and Matthew developed an Abdominal Compartment Syndrome where pressure compromises abdominal organ function and will cause death. The pressure was relieved by opening Matthew's abdomen and covering the gap with artificial material. Once again, Matthew survived. He was 5 months old.

How to feed Matthew without unhappy consequences became the ultimate awesome challenge. The difficulty was never overcome, his muscles to support respiration did not strengthen and a life connected forever to tubes, ventilator and catheters lay ahead. The family and caregivers chose to end his suffering and Matthew was taken home where for the last day of his life he was free of the technologies. He was held in the arms of his family where he died peacefully.

And who is Matthew? Matthew was our grandson who lived and died in Adelaide, Australia. My wife and I have contemplated again and again the little life of Matthew, all 7 months of it, minus one day, spent in an intensive care unit. Matthew became a hub for physicianship and intensive care. Matthew became the maker of links between the members of his extended family who came from different places on Planet Earth to be with him in Adelaide. Matthew was the sum of us, of the parents who made him, of the grandparents who made his parents, and so on back through the generations; Matthew in life and death is the sum of us all. His role on Earth, has been to make that sum much more than a bit of biological arithmetic and in so doing to bring out the best in expertise and compassion in all those who cared for him.

And what is the role for grandparents who fly half way around the world to be with grandson and family - day after uncertain day. My wife and I discovered the wisdom in Milton's sonnet on his own illness (3); we became aware that: They also serve who only stand and wait. Just being there, we discovered, was - to serve.

Matthew's story has multiple references to being reborn, an unmedical term but perhaps allowable when the person is an infant recently born and rescued back to life. Here, the term reborn implies there was a death or near death, as there would have been had there not been remarkable medical and surgical expertise and intervention.

To return then to the theme of an odyssey in life's journey; where there is a birth, a life, and then a death. You will have noticed that a death gave you the cadaver from which you learned some anatomy. Indeed that person gave you a gift of his or her body at the beginning of your education in medicine. From

another viewpoint, we have each been born and we have survived that perilous journey that began in the union of two haploid genomes. With the awareness of our own odyssey, of the journey, and of the end that comes to all of us, we are privileged to know about the gift of Life. And as I said earlier, with privilege comes responsibility. Each one of us will meet those responsibilities, and experience an odyssey, in our own individual way. Nonetheless, there are but two ways to approach the end, as was the case with Matthew; in one, we move on into eternal, ethereal life after this one ends; in the other, we return to the void from which we came. In each case, we did experience Life - a privilege never to be known by the inanimate objects of the universe from which we were made.

Whichever view I may hold about my own odyssey, I can still enrich my life and that of my patients, and of all other persons known to me, by making my life and their lives as meaningful as possible. In its simplest form, it can be done by being kind to others, to all living creatures and to life on Earth; and by opposing bad things; and in the physician's case, by healing the suffering associated with illness and disease.

This essay has the title: Who do I serve? Several types of service exist in this room at this moment: Service in medicine: to patients, families and communities. Service in education; to you and to the lifelong students that we are. Service in research: to the knowledge of tomorrow's medicine. Service to the unknowable: to the mystery of Life and Self.

Envoie

I mentioned my lack of humility when I graduated with my own medical degree. When I joined the faculty of McGill University some years later, I became aware that my life had to be lived forward and I became more humble because of the responsibilities I now had to family, myself, and my new appointment. I was also aware of global contexts which for you today are particular, and which for me then included the Cold War, the nemesis of nuclear war, the social crimes of segregation and poverty, the emerging war in Viet Nam and the assassination of a President, among other things. I needed a moral guide and I found him in the person and writings of Thomas Merton, a cloistered Trappist monk. He reached across denominational boundaries and cultures and touched people like me. Merton kept a diary and in it he describes an epiphany he experienced en route to an appointment with - his physician. He wrote (4): "At the corner of Fourth and Walnut, in the center of the shopping district, I was suddenly overwhelmed by the realization that I loved all those people, that they were mine, and I theirs, that we could not be alien to one another even though we were total strangers. It was like waking from a dream of separateness …". Merton goes on to describe "those people" in all their diversity and individuality, and ends with this extraordinary insight: "And if only everybody could realize this! But it cannot be explained. There is no way of telling people that they are all walking around shining like the sun. "

As I stand here, and gaze at you, I see extraordinary men and women. What is there to say to you, as you go forth to meet your patients, except this: Remember your humanity, listen to your patients, explain their mysteries to them, be kind, love your fellow beings, be informed, be humble and wise - and shine like the sun.

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REFERENCES

1. Eliot TS. Choruses from 'The Rock' in The Collected Poems 1909-1962. Faber and Faber. London, 1963. p. 161.
2. Eliot TS. East Coker: Four Quartets in The Collected Poems 1909-1962. Faber and Faber. London, 1903. p. 199.
3. Milton J. from the Sonnet On His Blindness.
4. Merton Th. Conjectures of a Guilty Bystander. Image Books, Doubleday. New York, 1968. p. 157-158.

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ORIGINAL ARTICLE

Troponin-I release after cardiac surgery with different surgical techniques and post-operative neurological outcomes

Norzeihan Jan Bappu*, Panangipalli Venugopal, Akhshay Kumar Bisoi, Pankaj S Mankad

ABSTRACT: Cerebral hypoperfusion during cardiopulmonary bypass surgery has been thought to be a factor in the aetiology of brain damage with evidence of post-operative neurological deficits. Cardiac-specific biomarkers such as troponin-I, troponin-T and CK-MB have been used extensively to predict myocardial injury and ischaemia. This prospective study investigateed the level of troponin-I release in both off-pump and CPB-technique CABG surgery, as well as postulated a relationship of troponin release and post-operative neurological outcome. A total of 44 adult patients undergoing coronary artery bypass graft (CABG) were enrolled into either an off-pump or on-pump groups, with 22 patients participating in each. Group A (on-pump) underwent myocardial revascularisation with CPB and cardioplegic arrest, while Group B (off pump) underwent beating heart surgery. The measurement of troponin-I is a 1-step enzyme immunoassay method, with specificity and sensitivity set at 0.4 ug/mL. Neurological assessment was done using the NIH Stroke Scale, and neuropsychologic assessment was assessed on cognitive function using modified Weschler Memory Scale, for which scores were standardized to achieve a composite measure of concentration. A set of statistical analysis was done to correlate troponin-I release with different surgical techniques of CPB and OPCAB. Although each independent technique showed a marked rise of troponin-I from baseline to 6 hours post-operatively, the difference in troponin release was not significant between the 2 groups at specified time intervals (p=0.124). There was however a significant correlation of troponin-I release with the number of grafts used in the surgery, irrespective of the type of grafts or surgical technique. None of the patients in either group showed any neurological or cognitive deficits presenting at day 3 and day 7 post-operatively. The findings of this study demonstrate that there is no significant short-term cognitive or neurological dysfunctions post-operatively, as indicated by troponin-I release in assessing the severity of myocardial injury.

INTRODUCTION

Cerebral damage associated with cardiac surgery has been extensively studied and this has been comprehensively reviewed (1-3). Cerebral hypoperfusion during cardiopulmonary bypass surgery has long been thought to be a factor in the aetiology of brain damage with evidence of post-operative neurological deficits (2,3). Cerebral injury may also occur in the early post-operative period, or alternatively, any intraoperative damage may be exacerbated by hypoperfusion at this stage.

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Previous studies have shown that cardiac surgery using extracorporeal circuit, also known as the cardiopulmonary bypass (CPB) technique, is associated with higher intraoperative myocardial damage and hence consecutively, worse cerebral hypoperfusion (4-6). There is a general consensus recently to undertake off-pump or beating heart coronary artery bypass graft (CABG) surgery with prospective aim that by avoiding CPB, cerebral and other complications should be limited. However, the incidence of cerebral complications after cardiac surgery varies considerably depending on the patients' demographical characteristics such as age, timing of the post-operative assessment, sensitivity of the assessment procedures and whether prospective or retrospective study procedures were used (7).

Current research showed that apart from a higher incidence of cerebral hypoperfusion and ischaemia, CPB produces numerous important causes of myocardial damage such as atriotomy, poor myocardial protection, duration of aortic cross-clamping, myocardial stunning; as well as myocardial ischaemia and infarction (7-9). During cardiac operations with CPB, the heart is arrested and protected using cardioplegia; during this period the heart is rendered ischaemic. At the end of CPB, the heart is reperfused and the cardiac action resumes. This reperfusion after ischaemic period produces myocardial damage and eventual necrosis. By contrast, during an off-pump cardiac surgery, the heart keeps beating and thus reperfusion injury is avoided.

Cardiac-specific biomarkers such as troponin-I, troponin-T and CK-MB, have been used extensively until recently, to predict myocardial injury and ischaemia (10-15). Troponin-I is solely confined to the myocardium and has been shown to be a highly specific marker for the detection of myocardial injury.

The aim of this prospective study was to investigate the level of troponin-I release in both off-pump and CPB-technique CABG surgery, and determine whether there is a significant myocardial injury associated with CPB, as suggested by the literature. This study also scrutinised the relationship of troponin-I with post-operative neurological sequelae in both CPB and OPCAB groups.

METHODS

This study was carried out in Department of Cardiothoracic Surgery, All India Institute of Medical Sciences, with subsequent data revision done in the New Royal Infirmary of Edinburgh. The study was approved by the Indian Medical Research, New Delhi.

A total of 44 adult patients undergoing coronary artery bypass graft (CABG) were enrolled into either an off-pump or on-pump groups, with 22 patients participating in each. Group A (on-pump) underwent myocardial revascularisation with CPB and cardioplegic arrest, while Group B (off pump) underwent beating heart surgery. Age boundaries were set at 16 and 85 years. On preoperative admission, the study was fully discussed with the patient, clerking on history and clinical examination performed. Pre-operative documentation included patient's age, gender, patient's pathology, operation planned, anti-platelet therapy given within seven days, pre-operative anti-coagulation and bleeding history. The inclusion criteria for patients in the study were; stable angina not suitable for balloon angioplasty or stenting, with two or more vessel disease. Exclusion criteria were the inability to provide informed consent, acute infections, severe ongoing neurological dysfunctions, impaired left ventricular fraction with ejection fraction of less than 30%, recent myocardial infarction within 1 month, acute renal failure, previous stroke or transient ischaemic attack, coagulopathy, emergency/ redo surgery and surgical re-exploration. This study conforms to the Declaration of Helsinki as regards medical research on human subjects as well as local ethical requirements.

Patient management

Standard monitoring was instituted prior to surgery; arterial line, central venous pressure, ECG, urinary catheter and nasal temperature.

All previous cardiac medications were continued up to the day of surgery, except aspirin and clopidogrel, which were stopped a week before the operation. Anaesthetic agents used were kept standard for all patients in both groups. Intravenous anaesthesia with propofol infusion 3mg.kg.hour and fentanyl 1 mg/kg/min were given at induction. Neuromuscular blockage was achieved by pancuronium bromide 0.15 mg.kg and lung ventilation was maintained as normocapnia with oxygen and air, without positive end expiratory pressure (PEEP).

Intraoperative evaluations were recorded on haemodynamic stabilility of the patients, the type and number of grafts used, the duration of the surgery, and specifically in CPB group, the duration of the CBP and aortic cross-clamp time.

Body surface area was calculated as a variable in patient demographic data, using the Dubois and Dubois Formula:

$$\text{Body surface area } (m^2) = 0.20247 \times \text{height } (m)^{0.725} \times \text{weight } (kg)^{0.425}$$

Operative technique

Standard open-heart technique was performed for all patients through total median sternotomy. In patients

undergoing surgery with CPB, heparin was added to the pump prime at a concentration of 1iu/ml. Prior to the institution of cardiopulmonary bypass (CPB) heparin was administered to the patient at a dosage of 300iu/Kg sufficient to raise the accelerated clotting time (ACT) to above 480 seconds. Whilst on CPB supplemental heparin was administered as required to maintain the ACT above this level. CPB was established with a roller pump, the use of a flexible venous reservoir with vent and cardiotomy suction. Systemic cooling was carried out to 28-32 C. Cold blood cardioplegia was used following application of the aortic cross clamp to achieve cardiac arrest. Once rewarming to 37 C was completed and CPB discontinued, protamine sulphate was given to reverse systemic heparinisation. Where the ACT remained above 140 seconds supplemental protamine was given. All pump blood remaining, except for that contained within the extra-corporeal circuit, was returned to the patient. After weaning from CPB, mean arterial pressure was maintained above 60 mmHg with appropriate vasoactive drugs.

In group A, the proximal grafts anastomoses were performed during aortic cross-clamp, and distal anastomoses followed subsequently. For off-pump group (Group B), Octopus device stabiliser were used only once during the graft anastomoses, with mean arterial pressure always greater than 65mmHg throughout the surgery to maintain haemodynamic stability. Heparin was administered at dosage of 1 mg/kg, protamine sulphate was not given for reversal of heparinisation. The temperature was set to be normothermia at 36 C. Intraoperative time was recorded from the beginning of sternotomy until the end of last distal anastomoses, whereas the surgery time was defined from the start of induction until transfer to the intensive care unit.

Thoracic drains were placed in the mediastinum, left and right pleural cavities where required. Post-operative suction was maintained at 20cm/H2O. All red cell transfusions were carried out as per local protocol. Crystalloid was given in the intensive care at a rate of 0.5mls/Kg with colloid administered where required.

Troponin-I Measurements

The measurement of troponin-I is a 1-step enzyme immunoassay method, with specificity and sensitivity of 0.4 ug/mL. The specificity with minimum value above 0.4ug/ml is necessary to indicate positive value. Serial measurements were taken at specified time from the arterial line. For patients undergoing surgery with CPB, measurements were taken at induction, 20 minutes after the start of CPB, at skin closure, 6 hours and 24 hours post-operatively. In OPCAB group, measurement was taken at induction, after the distal anastomosis of the graft conduits, at skin closure, 6 hours and 24 hours post-operatively. During the surgery, inspection was made on the condition of the aorta; patients who presented with abnormalities such as atherosclerotic plaque were excluded from the study.

Pre-operative and post-operative evaluations

Post-operative assessment was recorded into 2 components at day 3 post-operatively: 1) general observation on duration of ICU stay, post-operative ECG changes and re-exploration; 2)neurologic and neuropyshologic assessment. Neurological assessment was done using the NIH Stroke Scale, with patient diagnosed with acute neurological dysfunction if the criteria is above 10 (total score of 22). Any abnormal score would indicate cognitive dysfunction post-operatively, provided the baseline score at pre-operative was normal.

A standardized neurologic examination was done using the NIH Stroke Scale which assessed mentation, cranial nerve function, motor power, reflexes, sensation/cerebellar function, and gait, with 14 individual elements graded on a scale from 0 to 3 for a possible total of 42 was performed the day before the surgery. A score of more than 10 on total baseline assessment was identified as indicating preoperative neurologic dysfunction. Neuropsychologic assessment was done on cognitive function of the patient using modified Weschler Memory Scale, for which scores were standardized and averaged to achieve a composite measure of concentration.

RESULTS

Clinical characteristics

The patients' demographic data are shown in Table-2. A total of 44 patients were recruited for the study. One patient in CPB group had to be re-explored due to massive bleeding at day 1 post-operatively. None of the other patients in both groups had any serious bleeding through nose, gastrointestinal tract or urine catheter.

Serial troponin-I measurements

Below is the troponin values at each time interval of induction, intraoperative (20 minutes after start of CPB in CPB group, after distal anastomosis in OPCAB group), at skin closure, 6 hours and 24 hours post-operatively.

Table 1. Demographic and pre-operative data (n=22 in each group)

Variable	OPCAB group	CPB group	p value
Age	59.6± 8.5	59.1± 9.1	NS
Sex	13 males (60%),	15 males (70%),	

	9 females (40%)	7 females (30%)	NS
Weight	67.0 ± 7.2 kg	65.9 ± 8.2 kg	NS
Height	163.5 ± 7.9 cm	161.7 ± 8.0 cm	NS
Body surface area (m^2)	1.57±0.83	1.60± 0.26	NS
Preoperative ejection fraction	60% ± 0.3	59% ± 0.1	NS
Preoperative myocardial infarction	7	9	
X-Clamp	-	35.1 ± 10.6 minutes	
CPB time	-	56.6 ± 17.9 minutes	
Minimum Temp		31.7 ± 1.5 ^{O}C	
Max rewarming Temp		37.2 ± 0.32 ^{O}C	
Prothrombin time	1	1	NS

Table 2. Intraoperative and Post-operative Data

Variables	**OPCAB**	**CPB**
LIMA graft	22	22
Saphenous vein grafts	20	21
Grafts anastomoses per patient	3.2 ± 0.5	3.8 ± 0.1
Ventilation time (min)	38.4 ± 13	45.7 ± 20
Post-operative ejection fraction (%)	52% ± 0.2	56% ± 0.3
Sternal infection	2	1
Leg wound infection	1	1
Length of ICU stay (days)	1.5 ± 0.8	1.6 ± 0.5
Length of total hospital stay (days)	7.6 ± 2.0	6.6 ± 1.8
7-day mortality	0	0

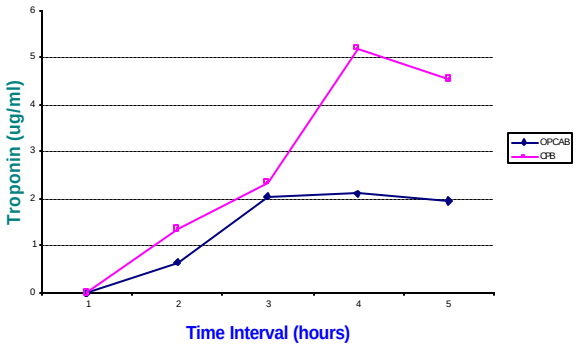
Table 3. Troponin-I values for both groups

Time Interval	**OPCAB (ug/ml)**	**CPB (ug/ml)**
Induction	0 ± 0	0±0
Intra-operative	0.65 ±0.85	1.35± 0.75
Skin closure	2.05 ±1.57	2.35 ±1.16
6 hours	2.10± 1.56	5.20 ±6.10
24 hours	1.95 ± 1.69	4.55 ± 5.67

Another set of analysis was made to see the correlation of troponin-I with different surgical techniques of CPB and OPCAB. Surprisingly, although each independent technique showed a marked rise of troponin-I from baseline to 6 hours post-operatively, the troponin release was not significant between the 2 groups at specified time intervals (p=0.124). Hence, when troponin-I is used as a cardiac biomarker for myocardial injury, troponin release in both groups do not reflect whether one technique is superior to the other based on short term cardiac clinical outcomes. In CPB group, there was no significance between post-operative troponin release with the duration of CPB or the aortic cross-clamp time (p>0.05).

Troponin level rise was almost uniform in both groups. This exception was noted in one patient in CPB group, where her post-operative 6 hours level was 22ug/ml. This patient had severe syncope preceded by palpitation 2 weeks prior to surgery, diagnosed as sick

Fig-1:Troponin-I Level at Specified Time Intervals



sinus syndrome and was put on temporary pacemaker up to the day of operation. The patient had bilateral renal artery stenosis and 2 episodes of myocardial infarction within a year prior to surgery. Although her baseline troponin-I was undetected, it was concluded that her co-morbidity prior to surgery contributed to significant myocardial injury intra-operatively.

Number of grafts and troponin-I release

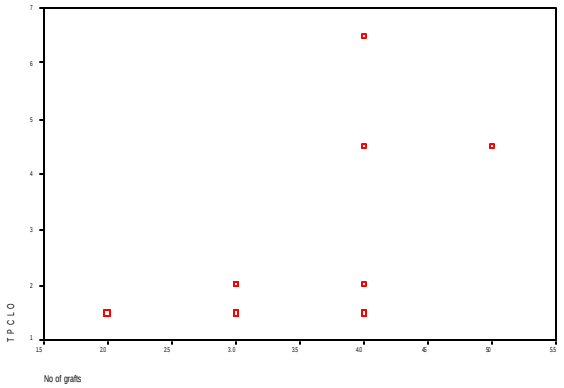
There was a significant correlation of troponin-I release with the number of grafts used in the surgery, irrespective of the type of neither the grafts nor the surgical technique. Graph below shows the statistical correlation between the number of grafts and the troponin release at 6 hours post-operatively. (Figure 2; 60% Pearson Correlation with p=0.005).

Post-operative evaluations

On general observation, there was a longer ICU stay

in patients with higher troponin release at 6 hours after closure (Pearson Correlation 79.2%, $p<0.05$). However, upon specific observations, it was noted that the length of ICU stay was not entirely determined by patients' haemodynamic stability, but also dependent on bed availability and date of transfer to the ward. Therefore, other factors should be kept into considerations before troponin is used as a sole predictor to determine patients' haemodynamic stability and length of ICU stay.

Patients in both groups underwent thorough neurologic and neuropsychologic clinical assessment at day 3 and day 7 after surgery. None of the patients in both groups showed any neurological deficits or cognitive deficits presenting post-operatively. This information indicates that any adverse effects on myocardial injury are normalised and were not followed



by any acute sequelae, representing deficit of operative procedures. With this negative finding on acute neurological outcomes, there was no significant relationship on biochemistry evaluation of troponin-I with acute post-operative neurological outcomes. Long term neurological outcome was not however being carried out for the purpose of this study.

DISCUSSION

Although the current consensus is with renewed interest and in favour of OPCAB technique in cardiac surgery, there has always been a debate on which surgical technique is more superior to another, in reducing the morbidity and mortality owing to myocardial revascularisation. One definite advantage of OPCAB is with increasing surgical demand; coronary operations could be performed at a lower cost without the expenses of a cardio-pulmonary bypass machine. However, a major concern on undertaking an off-pump approach is the obvious difficulty of performing the coronary anastomoses on the beating heart, with an increased risk of intraoperative myocardial ischaemia and suboptimal anastomoses performed (17). It goes without saying that achieving complete revascularisation should be the main priority of the surgery irrespective of the technique, as incomplete anastomoses of the grafts is significantly associated with post-operative mortality rate, perioperative myocardial infarction, and low cardiac output (17, 18). It is also important to consider other factors when choosing surgical procedure to be performed; this include surgeon's degree of expertise, patient population and their pre-existing comorbidities.

Biochemical markers have been used extensively to identify the mechanism of myocardial injury associated with surgical technique and the post-operative neurological sequelae, for patients who have had cardiac surgery performed with or without CPB. Recent literature suggests the superiority of OPCAB technique versus CPB, with relations to reducing morbidity and mortality associated with myocardial injury and cerebral hypoperfusion associated with the use of extracorporeal circuit of CPB (4, 5). Hypoperfusion during CPB is hypothesised to be related to microembolism and inflammatory changes that lead to increase in blood-brain barrier permeability, resulting in cerebral oedema. Hence, this study was carried out to confirm the previous results and to determine if there are any acute post-operative neurological deficits in CPB group.

The finding of this study does not support the current consensus, as we found that although there is a definite rise of troponin-I in both groups 6 hours after sternal closure, there is no significant difference in troponin release between CPB and OPCAB groups. It is important to note that there are multiple factors involved in contributing to inflammatory injury, apart from CPB, such as surgical trauma, ischaemic-reperfusion injury and thrombin activation (19). Surgery alone may activate haemostatic responses, activation of immune mechanisms and inflammatory responses mediated by the release of various cytokines and chemokines. Hence as seen in this study, the rise in troponin was almost uniform post-operatively in both group, with definite evidence of myocardial injury as the result of surgery itself.

With respect to inflammatory response, it is difficult to draw a conclusion on the extent of myocardial injury based on biochemical parameters alone, as there are other several confounding factors that may interplay in determining the ultimate haemostatic derangement. The threshold for inflammatory mediator release is also determined by patient individual risk stratification, protocol of heparin and protamine administration, anaesthesiologic techniques, and the expertise of the surgeon operating the cases. Hence troponin rise in this study does not indicate a direct correlation between the inflammatory response and the actual physiologic

mechanisms.

The study by Ascione et al suggests that complement activation of IL-6 is similar in both off-pump and on-pump patients after the cardiac surgery (20). This evidence is important to support the concept that surgical injury per se triggers release of acute-phase reactants, with possible impact on clinical consequences.

On a positive note, the statistical analysis however shows that irrespective of the surgical procedure, there is a significant positive correlation between the number of grafts performed in the surgery with 6-hour post-operative troponin-I release. (60% Pearson Correlation with p=0.005). Considering that the duration of the surgery increases on linear pattern with the number of grafts for each case, it is not surprising that myocardial injury is significantly higher in relation to the actual operation time, and the extent of anastomoses done directly on the myocardium. There is no significant difference between the troponin release and the type of grafts performed, such as LIMA, saphenous vein artery or radial grafts.

The evaluation of postoperative morbidity shows positive correlation between the rise of troponin after 6 hours post-operatively and the length of ICU stays in both groups of patients. Despite the optimism to use troponin as a biomarker for acute post-operative neurological deficit, the population of the study did not show any acute, evolving neurological symptoms as the result of the surgery. More follow-ups are needed to investigate whether these patients may show significant clinical signs on long term outcome. It should be emphasised that apart from clinical evaluation, there is a lack of effective methodology or marker for assessing neurologic and cognitive dysfunctions after cardiac surgery.

At present, more analysis is needed to explore the surgical complications of these patients, in terms of graft patency for CPB versus OPCAB groups, and also long term prospective neurological outcome after CPB-technique, as suggested by previous studies. Major postoperative complications such as in-hospital mortality was rare, hence large cohort studies would be needed to identify those aspects between the two groups in order to achieve positive statistical differences.

The findings of this study demonstrate that there is no proven significant short term cognitive or acute neurological dysfunctions post-operatively, as indicated by troponin-I in assessing the severity of myocardial injury, within the scope of our research. Although this contradicts the popular belief that off-pump surgery reduces morbidity and mortality rate, these observations may encourage a larger cohort in the future to improve our understanding on the actual mechanism of myocardial injury, without omitting the judicious stratification of the patient's pre-existing clinical condition in determining the most appropriate surgical technique for their own optimal outcome.

REFERENCES

1. Kuroda Y, Uchimoto R, Kaieda R, Shinkura R, Shinohara K, Miyamoto S, Oshita S, Takeshita H. Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. Anesthesia & Analgesia. 1993; 76:222-227.
2. Millar SM, Alston RP, Andrews PJ, Souter MJ. Cerebral hypoperfusion in immediate postoperative period following coronary artery bypass grafting, heart valve, and abdominal aortic surgery. British Journal of Anaesthesia. 2001; 87:229-236.
3. Fearn SJ, Pole R, Wesnes K, Faragher EB, Hooper TL, McCollum CN. Cerebral injury during cardiopulmonary bypass: emboli impair memory. Journal of Thoracic & Cardiovascular Surgery. 2001; 121:1150-1160.
4. Schneider M, Valentine S, Hegde RM, Peacock J, March S, Dobb GJ. The effect of different bypass flow rates and low-dose dopamine on gut mucosal perfusion and outcome in cardiac surgical patients.[erratum appears in Anaesth Intensive Care 1999 Apr;27(2):228]. Anaesthesia & Intensive Care. 1999; 27:13-19.
5. Taylor KM. Central nervous system effects of cardiopulmonary bypass. Annals of Thoracic Surgery. 1998; 66:Suppl-4.
6. Stump DA, Rogers AT, Hammon JW, Newman SP. Cerebral emboli and cognitive outcome after cardiac surgery. Journal of Cardiothoracic & Vascular Anesthesia. 1996; 10:113-118.
7. Furlan AJ, Sila CA, Chimowitz MI, Jones SC. Neurologic complications related to cardiac surgery. Neurologic Clinics. 1992; 10:145-166.
8. Utley JR. Techniques for avoiding neurologic injury during adult cardiac surgery. Journal of Cardiothoracic & Vascular Anesthesia. 1996; 10:38-43.
9. Kuroda Y, Uchimoto R, Kaieda R, Shinkura R, Shinohara K, Miyamoto S, Oshita S, Takeshita H. Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. Anesthesia & Analgesia. 1993; 76:222-227.
10. Nagurney JT, Heredia O, Sane S, Lewis SC, Chang IK. A comparison of three methods for defining acute myocardical infarction. Academic Emergency Medicine 10(5):534. 2003.
11. Davis GK, Nimrod M. Cardiac biomarker usage in the West Indies. West Indian Medical Journal. 2003; 52:260-261.
12. de Lemos JA, Morrow DA. Combining natriuretic peptides and necrosis markers in the assessment of acute coronary syndromes. Reviews in Cardiovascular Medicine. 2003; 4:Suppl-46.
13. Lewandrowski K, Chen A, Januzzi J. Cardiac markers for myocardial infarction. A brief review. American Journal of Clinical Pathology. 2002; 118:Suppl-9.
14. Gensini GF, Fusi C, Conti AA, Calamai GC, Montesi GF, Galanti G, Noferi D, Carbonetto F, Palmarini MF, Abbate R, Vaccari M. Cardiac troponin I and Q-wave perioperative myocardial infarction after coronary artery bypass surgery. Critical Care Medicine. 1998; 26:1986-1990.
15. Barron JT. Cardiac troponin I and non-Q-wave myocardial infarction: how useful is it after coronary artery bypass surgery? Critical Care Medicine. 1998; 26:1936-1937.

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16. Fellahi JL, Gue X, Richomme X, Monier E, Guillou L, Riou B. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. Anesthesiology. 2003; 99:270-274.
17. Ascione R, Caputo M, Angelini GD. Off-pump Coronary Aretry Bypass Grafting: Not a Flash in the Pan. Annals of Thoracic Surgery. 2003; 75:306-13.
18. Angelini GD et al. Early and midterm outcome after off-pump and on-pump surgery in BEating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet. 2002; 359:1194.
19. Czerny M et al. Inflammatory response and myocardial injury following coronary artery bypass grafting with or without cardiopulmonary bypass. European Journal of Cardiothoracic Surgery. 2000; 17:737-742.
20. Ascione R et al. Inflammatory Response After coronary revascularisation with or without cardiopulmonary bypass. Annals of Thoracic Surgery. 2000; 69:1198-204.

ORIGINAL ARTICLE

Ventilatory management in extremely low birth weight infants

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ABSTRACT: The improvement in survival in premature infants associated with the evolution of mechanical ventilation has been accompanied by an increase in ventilator induced lung injury. High frequency ventilation has been shown to reduce the incidence of ventilator induced lung injury and hence chronic lung disease in the very low birth weight infant. The evolution in understanding how to best use high frequency ventilation in this population has prompted us to ask whether similar strategies to optimize lung volumes on conventional mechanical ventilation can minimize chronic lung disease in the neonate. We retrospectively reviewed the medical charts of 51 extremely low birth weight infants born in Kingston, Ontario in two epochs, 1990 to 1991 and 1999 to 2000, for ventilatory strategy and outcome. From our review, it is clear that surfactant therapy rapidly changes lung mechanics by improving pulmonary compliance and that lung damage may result if there are not changes in the ventilatory management to reflect the altered compliance. Early ventilation strategies during the apparently stable "honeymoon period" in a patient with respiratory distress syndrome (RDS) has significant implications on long term morbidity. In the era prior to the use of surfactant, 30% of infants died and 40% developed chronic lung disease (CLD). Immediately following the use of surfactant , mortality was reduced to 18%, however, the incidence of CLD increased to 78%. In the most recent era, following 10 years of experience with surfactant and mechanical ventilation, morbidity was 17% and CLD 21%. This study demonstrates that a particularly crucial time is in the immediate period following surfactant administration. The use of lower peak inspiratory pressure (PIP) and mean airway pressure (MAP) over the first 24 hours and an increase in the use of synchronous intermittent mandatory ventilation (SIMV) was associated with an improved outcome. The challenge remaining is to determine how to best utilize a conventional mode of ventilation to best optimize lung volume and protect the immature lung.

INTRODUCTION

Prior to the mid 1960s, mechanical ventilators were designed to provide alveolar ventilation and additional oxygen to patients suffering from neurological impairment. In 1963, physicians at the Hospital for Sick Children in Toronto, ventilating infants with a Bird Mark VIII machine, achieved their first survivor without air leak or cerebral abnormalities (1). Soon thereafter, low levels of positive end-airway pressure (PEEP) were used to overcome the gradual decline in functional residual capacity (FRC) and minimize atelectasis. PEEP effectively stents open the lung to prevent collapse at the end expiratory point. Similarly,

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continuous positive airway pressure (CPAP) during mechanical ventilation stents open the lung throughout the entire respiratory cycle, preventing collapse and permitting lower pressures to be used for movement of gas. CPAP and PEEP became mainstays of mechanical ventilation during acute lung injury. In the early 1970s, intermittent mandatory ventilation (IMV) that delivered a certain volume at specific time intervals interspersed with the patient's respiratory efforts was the common method of neonatal ventilatory support.

Positive pressure ventilation (PPV) utilizes supraphysiologic pressues to induce the flow of gas into the lung. While PPV reduced mortality, an increase in morbidity was seen amongst survivors, in part related to ventilator management of the high pressures. In 1974, Webb and Tierney demonstrated that PPV could induce lung injury manifested by edema hemorrhage and hyaline membrane formation (2). Asynchrony between the ventilator delivered volume and spontaneous breathing is common during conventional intermittent mandatory ventilation and may result in irregular systemic and cerebral flow patterns, suboptimal gas exchange, barotraumas, airleak syndrome, pulmonary hemorrhage, intraventricular hemorrhage, periventricular leukomalacia, and chronic lung disease (1,3). These complications may be avoided by sedatives or muscle relaxants to minimize the infant's spontaneous breathing. Alternatively the ventilator rate and inspiratory time may be manipulated to be synchronous with spontaneous breaths. A third approach is patient-triggered ventilation in which the breath delivered by the ventilator is triggered by the early spontaneous breathing effort. There are two types of patient-triggered ventilation: assist control, where every spontaneous breath triggers a ventilator breath and synchronized intermittent mandatory ventilation (SIMV), where the ventilator is only triggered on selected spontaneous breaths (3). Infant ventilators may use one of several methods to detect spontaneous breathing. These include abdominal movement, thoracic impedance through electrocardiogram leads, and sensors of airway pressure or flow (4). Recent advances in neonatal conventional mechanical ventilation (CMV) include increased sensitivity and hence improved patient-ventilator synchrony, pressure limited machines, graphics, calculations of gas leak, tidal volume (Vt), minute ventilation, and flow volume loops. Additionally, impact of new methods of neonatal ventilatory management including pressure support, volume guarantee, and non-invasive ventilation such as the use of continuous positive airway pressure (CPAP) are continually being studied (5-7).

The most important advancement in neonatal care was the utilization of surfactant. Surfactant proteins were isolated and characterized in the 1970s and 1980s and the genes responsible for these proteins were cloned and sequenced (8). The clinical benefit from surfactant comes from its ability to lower alveolar surface tension and therefore increase compliance, increase stability and maintain small airway patency.

"PROTECTIVE LUNG STRATEGY" - HIGH FREQUENCY OSCILLATORY VENTILATION VERSUS CONVENTIONAL VENTILATION

High frequency oscillatory ventilation (HFOV) is a ventilatory strategy using low tidal volumes with low phasic pressure changes and supraphysiologic ventilatory frequencies. While the initial major HFOV study provided disappointing results, this has been attributed to some misunderstandings of how HFOV should be used (9). The Provo Multicenter Early High-Frequency Oscillatory Ventilation Trial concluded that when used early with a lung recruitment strategy, HFOV after surfactant replacement resulted in clinical outcomes consistent with a reduction in both acute and chronic lung injury (10). Reimensberger et al (11). managed 32 very low birth weight (VLBW) infants with first intention HFOV and compared this group to 39 historical controls managed with CMV and found that early use of HFOV with lung volume optimization significantly shortened the duration of respiratory support and improved pulmonary outcome. In a more recent study, Courtney et al. demonstrated a small but significant benefit of HFOV versus SIMV in terms of the pulmonary outcome of VLBW infants (12). In this study, HFOV did not result in an increase in the occurrence of other complications of premature birth.

It is apparent from the early use of HFOV that the outcome is dependant on the strategy applied and the individual disease process. If the lung is expanded and cyclical collapse is prevented, underlying disease process(es) may recover, limiting further inflammatory response (and hence chronic lung disease (CLD)) and potentially support endogenous surfactant production. Ventilator induced lung injury (VILI) and hence CLD may be reduced by using HFOV with a lung recruitment approach. The question then becomes: can similar results be achieved by using CMV with an "open lung" in VLBW neonates? Similarly, adult studies involving patients with acute respiratory distress syndrome and in intensive care demonstrated that protective strategies with an open lung approach (PEEP above the lower inflection point on the static pressure-volume curve, low tidal volume, permissive hypercapnia) in comparison to CMV resulted in improved survival, higher rate of weaning from mechanical ventilation and a lower rate of ventilator induced lung injury (13-15). Vazquez de Anda et al. (16) used an animal study to

demonstrate that CMV with sufficient level of PEEP and small driving pressure amplitudes is as effective as HFOV in maintaining optimal gas exchange, improving lung mechanics, and preserving exogenous surfactant. Thome demonstrated that HFOV versus CMV with high RR and low peak inspiratory pressures resulted in no difference in lung injury (17). Other ventilatory factors thought to play a role in outcome are the peak inspiratory pressure (PIP) and the mean airway pressure (MAP). HFOV uses lower PIP and MAP than does CMV and recent trends have been towards lowering pressures in CMV in an effort to minimize lung trauma.

PURPOSE

There is currently minimal published Canadian data examining the ventilation experience in extremely low birth weight infants. The purpose of this study is to examine how CMV ventilation strategy has changed over time in a Canadian tertiary level neonatology unit and to determine how these changes have affected patient outcome.

METHODS

Study design

This study was conducted as a retrospective chart review of two epochs, 1990-1991 and 1999-2000. The use of surfactant in neonates with respiratory distress syndrome (RDS) was begun in Kingston, Ontario in July 1990. The eligible infants from these two epochs were assigned to one of three groups: Group 1 - Immediately pre introduction of surfactant - 1990; Group 2 - Immediately post introduction of surfactant - 1990-1991; Group 3 - Ten years post introduction of surfactant - 1999-2000. The two different time periods were chosen in order to examine how ventilator strategies on CMV have changed 1) following the introduction of surfactant, and 2) with time. The examination of data from both the pre and post surfactant era as well as a comparison to more recent techniques contributes to the novelty of the data presented.

Patient inclusion criteria

Eligible patients: all live-born, mechanically ventilated neonates weighing less than 1000 grams who were admitted to the neonatal intensive care unit in Kingston, Ontario during the two epochs .

Data collection

For all eligible infants, the ventilator settings were recorded for the first 72 hours of life. The median value of the ventilator settings was calculated over the first three 24 hour periods of life and the ranges and standard deviations were recorded. Outcomes of interest were:

1) Ventilator settings during hours 0 - 72 of life
2) Incidence of bronchopulmonary dysplasia (BPD) as defined by use of supplemental oxygen at 36/40 weeks corrected gestational age
3) Total duration of O2 dependence
4) Total duration of mechanical ventilation
5) Incidence of severe intraventricular hemorrhage (i.e. grade III/IV)
6) NICU mortality.

STATISTICAL ANALYSIS

An unpaired t-test was used for parametric data. Categorical data were analysed by means of a Fisher's exact test or Chi2 analysis as appropriate. For all testing, a p value of < 0.05 was accepted as significant. Comparisons were made between:

1) Group 1 and Group 2
2) Group 2 and Group 3

RESULTS

There were 51 eligible neonates, all of whom were included in the study. All 51 of neonates were intubated and ventilated. One child from group 2 was transferred from Kingston and was considered lost to follow up.

Group 1 (n = 10; 4 male (m) and 6 female (f))
Group 2 (n = 11; 6 m and 5 f)
Group 3 (n = 30; 11 m and 19 f)

There was no statistical difference between Groups 1 and 2 or Groups 2 and 3 with the exception of surfactant use, which was by design (Tables 1 and 2).

The neonates in Group 2 received an average of 1.5 doses of surfactant compared to the neonates in Group 3 receiving surfactant who received an average of 1.9 doses.

Table 1. Comparison Between Groups 1 and 2

	Group 1 (n=10)	Group 2 (n=11)	P Value
Mean BW (g)	798 (480-950)	823 (660-980)	NS
Mean GA (wks)	26.4 (23-29)	26.7 (24-30)	NS
Male	4	6	NS
Female	6	5	NS
Surfactant	0	11	P<0.0001
Pre Natal Steroids	3	8	NS

Table 2. Comparison Between Groups 2 and 3

	Group 2 (n=11)	Group 3 (n=30)	P Value
Mean BW (g)	823 (660-980)	778 (519-979)	NS
Mean GA (wks)	26.7 (24-30)	26 (24-32)	NS
Male	6	11	NS
Female	5	19	NS
Mech. Ventilated	11	30	NS
Surfactant	11	24	NS
Pre Natal Steroids	8	13	NS

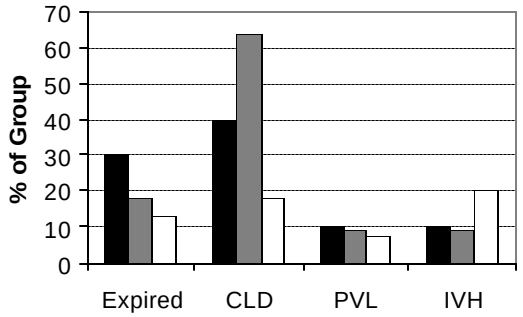

Figure 1: Outcomes in Groups 1, 2, and 3

Respiratory morbidity

In Group 1, all infants were ventilated on an intermittent mandatory mode (IMV). In this epoch, IMV was available on both the Bear Cub and Sechrist ventilators. Median duration of mechanical ventilation was 21 days (1-109) with a standard deviation of 35.6 days. In Group 2, all infants were ventilated on IMV. Median duration of mechanical ventilation was 28 days (2-75) with a standard deviation of 20.7 days.

In Group 3, 9 infants were ventilated solely on IMV, 10 infants were ventilated solely by synchronized IMV mode (Babylog), and 11 were ventilated on a combination of IMV and/or SIMV and/or assist control (AC). The median duration of mechanical ventilation in this group was 30.0 days (1-73) with a standard deviation of 19.9 days. Table 3 records the ventilator parameters used in the three groups. Of note, there was not a significant difference in PIP and MAP between groups 1 and 2 in the first 24 hour period whereas there was a significant difference in these variables between groups 2 and 3 over the first 24 hours. There were ventilator settings recorded in Group 3 that were not noted in the earlier time periods. These include inspiratory time (IT) and inspiratory to expiratory ratio (I:E). The inspiratory times for the first, second, and third 24 hours periods were 0.47 (0.40-0.53), 0.47 (0.42-0.55), and 0.48 (0.42-0.55) respectively. The I:E for the first, second, and third 24 hour periods were3.5 (1.9-10.4), 4.7 (1.6-10.7), and 3.5 (1.2-10.7) respectively. Tables 4 and 5 compare duration of ventilation and oxygen dependence between the three study groups.

Morbidity and mortality

In the pre-surfactant era Group 1, 30.0% (3 of 10)

Table 3. Ventilator Parameters in Groups 1, 2, and 3

	Group number	0-24 Hours	24-48 Hours	48-72 Hours
PIP	1	25.5 (18-35)	26.8 (18-43)	30.0 (20-43)
	2	23 (18-30)	20 (14-23)	20 (18-25)*
	3	18 (13.5-24)#	16 (12-22)	16 (12-23)#
MAP	1	10.5 (5.5-12.5)	12 (7.5-17)	12 (9-16)
	2	9 (7-21)	7 (6-10)*	6.5 (6-10)*
	3	7.6 (4-10.5)#	6.8 (3-11)	7.2 (3-12)
RR	1	55 (15-95)	67.5 (30-130)	72.5 (36-120)
	2	35 (20-60)	22 (10-60)	35 (10-45)
	3	27.5 (15-40)#	22.5 (10-45)	30 (10-60)
PEEP	1	5 (4-5)	5 (4-6)	4.5 (4-6)
	2	5 (4-6)*	5 (4-6)*	5 (4-5)*
	3	5 (4-5)	5 (4-7)	5 (3-6)
CO_2	1	44.5 (25-56)	49 (33-58.5)	45 (34-62)
	2	37 (26-69)	38 (30-50)*	39 (30-48)
	3	37.1 (29.7-45.9)	43.1 (32.2-73.3)	38.8 (32.0-63.6)

* significant difference between groups 1 & 2
# significant difference between groups 2 & 3

infants did not survive to discharge. The mean age at death in these infants was 10 (1-18) days. The cause of death was respiratory failure in all three cases. In Group 2 (ie since the introduction of surfactant use) 18.1% (2 of 11) of infants did not survive to discharge. The mean age at death in this group was 4.5 (2-7) days. Causes of death were respiratory failure and pulmonary hypoplasia. In Group 3, 16.7% (5 of 30) of infants expired. The mean age at death in this group was 23.3 (2-64) days. Causes of death included periventricular leukomalacia, intraventricular hemorrhage, necrotizing enterocolitis, candida sepsis, gram negative sepsis, and respiratory failure. Figure 1 illustrates the comparisons of these outcomes amongst the three study groups.

Table 4 Duration of Oxygen Dependence and Ventilation (Groups 1 and 2)

	Group 1	Group 2	P Value
Median O2 Dep (d)	45 (1-148)	58 (2-145)	0.8
Median O2 Dep (CGA)	34 (23-47)	36 (26-65)	0.3
Median Duration of Mech Vent (d)	21 (1-109)	28 (2-75)	0.7

Table 5 Duration of Oxygen Dependence and Ventilation (Groups 2 and 3)

	Group 2	Group 3	P Value
Median O2 Dep (d)	58 (2-145)	34.5 (1-73)	0.04
Median O2 Dep (CGA)	36 (26-65)	32 (26-41)	0.07
Median Duration of Mech Vent (d)	28 (2-75)	30 (1-73)	0.7

DISCUSSION

While the introduction of surfactant has significantly reduced the mortality from respiratory distress syndrome, chronic lung disease remains a significant problem in the extremely low birth weight infant (20.7% in 1999). By comparing extremely low birth weight infants who received surfactant (Group 2) versus those who did not (Group 1), it is possible to determine the effect of surfactant in decreasing the morbidity and mortality from respiratory distress syndrome. The observation between the two groups of patients born since the routine use of surfactant, i.e. one early in the surfactant era (Group 2) and a second cohort born ten years later (Group 3) were made in order to determine how changes in ventilatory management may affect neonatal outcome. It is clear that surfactant therapy rapidly changes lung mechanics by improving pulmonary compliance. However, it is evident that surfactant therapy alone does not decrease the incidence of chronic lung disease (40.0% incidence in Group 1 vs 77.8% incidence in Group 2). In group 1, higher PIP and MAP was required in order to overcome the very low compliance of the surfactant deficient lung. It is likely that the high pressures used contributed significantly to the incidence of chronic lung disease in this group. In group 2, the PIP and MAP were not significantly lower in the first 24 hours. While mortality was significantly lower, the incidence of CLD is substantially higher in the infants immediately following the introduction of surfactant (Group 2), when compared to Group 1. Although surfactant therapy improved lung compliance, in the absence of a significant decrease in pressures in the first 24 hours, damage to the lung occurred. This illustrates how even brief periods of a mechanical ventilatory strategy on CMV may cause lung injury and affect outcome in the presence of changing pulmonary compliance. In comparison to Group 2, the infants in Group 3 had a significantly lower mortality rate and incidence of CLD. This likely reflects the impact of a change in ventilator management given that there were no other significant baseline differences between these two groups. Evolution in ventilation strategies included an increase in the use of SIMV, lower PIP, and lower MAP. It is of significance that the PIP and MAP were statistically lower over the first twenty-four hour time period in Group 3. The lower PIP and MAP in Group 3, combined with advances in pressure/volume limitation, has the effect of limiting barotraumas and hence reducing the incidence of CLD. The duration of O2 dependence is also significantly lower in Group 3. This may reflect improvements in strategies to optimize lung recruitment. The fluid management regime and the incidence of patent ductus arteriosis were not reviewed during this study and should be included in future studies.

Following the results of this study, our question remains: how can CMV and surfactant therapy continue to be optimized? Certainly, all clinicians are aware that of the need to limit volutrauma. Proven strategies include minimizing the MAP, limiting the transalveolar pressure, using small amplitudes (Vt 4-6 ml/kg) and the use of high frequency oscillatory ventilation. However, are there other strategies that we can utilize during CMV that can further optimize patient outcome? Recent animal and human studies show that CMV may perhaps be just as effective as HFOV when an appropriate "protective lung strategy" is used (17,18,19). Froese et al. showed that early lung volume optimization preserves surfactant life span by both decreasing the rate of inactivation and allowing for endogenous production (20). From these data, it seems that a "lung

protective strategy" with early volume optimization and surfactant therapy is an effective approach. Possible strategies include using a high respiratory rate and hence inducing an auto PEEP, determining and implementing the optimal PEEP, early permissive hypercapnea, and using shorter, more physiological inspiratory times. Recent advances in ventilator technology such as pressure support, volume guarantee, volume support, and proportional assist modes are designed to limit lung injury in the VLBW neonatal population. A further approach may be to avoid mechanical ventilation altogether and use NCPAP as is suggested by the Scandinavian studies (7,21).

CONCLUSION

From these data we can conclude that while surfactant therapy has proven benefits in improving pulmonary mechanics, and hence the survival of neonates, equally important is the ventilation strategy used on the premature lung with changing compliance. From this study, it appears that surfactant therapy actually increased the risk of CLD in 1990-1991. Early ventilation strategies during the apparently stable "honeymoon period" in a patient with RDS has significant implications on long term morbidity. As demonstrated by this study, a particular crucial time is in the immediate period following surfactant administration. The learning curve experienced by clinicians in the years following the widespread use of exogenous surfactant has demonstrated a change towards acting on clinically apparent changes in the neonate, rather than a dependence on blood gas measurements and chest radiograph findings. This has been aided by more recent advances in ventilator technology (tidal volume and minute ventilation measurements) and non-invasive monitoring (transcutaneous CO2 measurements). The difficulty, as demonstrated by the "open-lung" studies by NIH, etc. in patients with ARDS, is to conduct randomized controlled trials comparing strategies in CMV in the neonate, in light of our evolving experience on how best to use a conventional ventilator (13,15). The goal now is to overcome these challenges and to continue to learn how best to utilize a "conventional" mode of ventilation to optimize lung volume and protect the immature lung.

REFERENCES

1. McGettigan MC, Adolph VR, Ginsberg HG, Goldsmith JP. New Ways to Ventilate Newborns in Acute Respiratory Failure. Pediatric Clinics of North America 1998; 45 (3): 476-509.
2. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. American Review of Respiratory Disease 1974; 110 (5): 556-65.
3. Bernstein G, Mannino FL, Heldt GP, et al. Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. Journal of Pediatrics 1996; 128 (4): 453-463.
4. Bernstein G. Syncrynous and patient-triggered ventilation in newborns. Neonatal Respiratory Diseases 3 1993; 6(5): 54-8, 66.
5. Van Marter LJ, Allred EN, Pagano M, et al. Do Clinical Markers of Barotrauma and Oxygen Toxicity Explain Interhospital Variation in Rates of Chronic Lung Disease? Pediatrics 2000; 105 (6): 1194-1201.
6. Avery ME; Tooley WH; Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987; 79 (1): 26-30.
7. Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birth weight infants in special-care units and neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilatin: gains and losses. Aca Paediatr Suppl 1997; 419: 4-10.
8. Kuroki Y, Voelker DR. Pulmonary surfactant proteins. Journal of Biological Chemistry 1994; 269 (42): 25943-25946.
9. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. New England Journal of Medicine 1989; 320 (2): 88-93.
10. Gerstmann DR, Minton SD, Stoddard RA, et al. The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1994; 98(6 Pt 1) 1044-1057.
11. Rimensberger PC, Beghetti M, Hanquinet S, Berner M. First intention high-frequency oscillation with early lung volume optimization improves pulmonary outcome in very low birth weight infants with respiratory distress syndrome. Pediatrics 2000; 105(6): 1202-1208.
12. Courtney SE, Durand DJ, Asseliln JM et al. High Frequency Oscillatory Ventilation versus Conventional Mechanical Ventilation for Very-Low-Birth-Weight Infants. New England Journal of Medicine 2002; 347 (9): 643-652.
13. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. New England Journal of Medicine 1998; 338: 347-354.
14. National Institutes of Health. NHLBI clinical trial stopped early: successful ventilator strategy found for intensive care patients on life support. National Institutes of Health news release. March 15, 1999.
15. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. New England Journal of Medicine 1998; 338(6): 355-361.
16. Vazquez de Anda GF, Gommers D, Verbrugge SJ. Mechanical ventilation with high positive end-expiratory pressure and small driving pressure amplitude is as effective as high-frequency oscillatory ventilation to preserve the function of exogenous surfactant in lung-lavaged rats. Critical Care Medicine 2000; 28 (8): 2921-2925.
17. Thome U, Kössel H, Lipowsky G, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. Journal of Pediatrics 1999; 135 (1): 39-46.
18. Johnson AH, Peacock JL, Greenough A, et al. High Frequency Oscillatory Ventilation for the Prevention of Chronic Lung Disease of Prematurity. New England Journal of Medicine 2002; 347 (9): 633-642.
19. Stark AR. High Frequency Oscillatory Ventilation to Prevent Bronchopulmonary Dysplasia - Are we there yet? (Editorials). New England Journal of Medicine 2002; 347 (9): 682-683.

20. Froese AB, McCulloch PR, Sugiura M et al. Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. American Review of Respiratory Disease 1993; 148 (3): 569-577.

21. Blennow M, Jonsson B, Dahlström A, et al. [Lung function in premature infants can be improved. Surfactant therapy and CPAP reduce the need of respiratory support]. Lakartidningen 1999; 96 (13): 1571-1576.

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ORIGINAL ARTICLE

An approach to compare the quality of cancellous bone from the femoral necks of healthy and osteoporotic patients through compression testing and microcomputed tomography imaging

Anthony Ciarallo*, Jake Barralet, Michael Tanzer, Richard Kremer

ABSTRACT: It is estimated that osteoporosis is responsible for about 300 000 hip fractures per year in the United States. Effective prevention of these fractures has been demonstrated using bisphosphonates. However, their mechanism of action has not been elucidated. Furthermore, the precise effect of bisphosphonates on the femoral neck and surrounding areas has never been studied. We are interested in establishing a protocol to analyze the bone quality of proximal femurs from patients treated with bisphosphonates. Following hip replacement surgery, the aim is to determine whether imaging and compression testing of cancellous bone from the discarded femoral necks can accurately assess the bone's microarchitectural and biomechanical properties, respectively. To validate the technique, it was first tested on an untreated population. A bone biopsy trephine was used to extract cylindrical cores of trabecular bone from the centre of femoral necks. Densitometry, microcomputed tomography, and compression testing were used to assess the quality of bone in these samples. The compressive strength was found to be directly proportional to the modulus (i.e. stiffness) of the samples, thus reproducing previous findings. The relative porosity and, to a lesser extent, the bone mineral density were capable of predicting the quality of cancellous bone. In conclusion, a protocol to analyze the bone quality in human femoral necks using μCT and biomechanical compression testing was successfully established. It will be applied in a clinical setting to analyze bones from bisphosphonate-treated patients following total hip replacement.

KEYWORDS: microcomputed tomography, biomechanics, bisphosphonates, femoral neck, cancellous, osteoporosis, hip fracture

INTRODUCTION

Osteoporosis is defined by the World Health Organization (WHO) as having a bone mineral density (BMD) of more than 2.5 standard deviations below the norm for healthy young adults (1). BMD, measured by dual-energy X-ray absorptiometry, is used as a bone mass index to predict the risk of fracture (1).

Osteoporotic bones are porous and fragile, thus making them more susceptible to fracture than healthy bones. In order to maintain a healthy skeleton, a steady-state of bone remodeling occurs in adults in which new bone is generated at the same rate that old bone is removed. The remodeling process is important for maintaining bone strength because it adapts the structure of bone to mechanical loads (2). In osteoporosis, the rate of bone resorption exceeds that of the formation, resulting in a progressive deterioration of bone mass and microarchitecture (2).

There are the two kinds of bone that comprise the

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skeleton are compact and cancellous (i.e. trabecular). Compact bone predominates in the appendicular skeleton and is designed to resist bending forces. On the other hand, cancellous bone is concentrated in the axial skeleton and is structured to resist compressive forces, including gravity. Since it is lighter and more porous than compact bone, cancellous bone provides more surface area for bone remodeling and is more metabolically active (2). Consequently, cancellous bone is more affected in osteoporosis (3).

One class of drugs aimed at preventing bone loss is bisphosphonates. Bisphosphonates, including alendronate and risedronate, are antiresorptive agents which are stable analogues of inorganic pyrophosphate and have a high affinity for hydroxyapatite crystals. They bind selectively to mineralized surfaces of bone to disrupt degradative osteoclast activity and promote apoptosis of mature osteoclasts (4). Bisphosphonates are also thought to prolong the life of osteoblasts by inhibiting apoptosis (5).

Alendronate and risedronate are highly effective in decreasing the risk of vertebral and hip fractures (6-8). But, it was also demonstrated that the observed increase in BMD in bisphosphonate-treated patients does not entirely account for the reduction in fracture risk (6). Therefore, the mechanism of action of bisphosphonates has not yet been elucidated. In fact, it is hypothesized that bisphosphonates may act by increasing bone mass, improving trabecular microarchitecture, and/or increasing secondary mineralization of the calcified matrix (9). Recently, more emphasis has been placed on the concept of "bone quality" which encompasses the microarchitectural and biomechanical properties of bone (10, 11).

It is estimated that osteoporosis is responsible for about 300 000 hip fractures per year in the United States (12). Recent studies have shown that hip-fractured patients rapidly lose bone density within 6 months after fracture, possibly because of the absence of weight bearing for 6 weeks post-operatively and the fact that peri-prosthetic bone loss rapidly occurs following hip arthroplasty (13). Since there is no standard of care for the prevention and the treatment of osteoporosis in these patients, our interest is to determine the best approach to prevent bone loss in this group. As the effect of bisphosphonates on the femoral neck and surrounding areas has not yet been assessed, we will analyze the bone quality of proximal femurs from treated patients that are discarded after hip replacement surgery. Prior to undertake these clinical trials, however, protocols must be established in an untreated population in order to properly assess the quality of bone.

This project aims to determine whether imaging and compression testing of cancellous bone from the femoral neck can accurately assess the bone's microarchitectural and biomechanical properties, respectively, and if together they will serve as a good index of bone quality.

MATERIALS AND METHODS

Twenty-two bovine (calf) femurs were obtained from a butcher (Boucherie Charcuterie Rivière des Prairies, Montreal, QC). Nineteen human proximal femurs were collected by Dr. Michael Tanzer (Montreal General Hospital, Montreal, QC) and Dr. William Fisher (Montreal General Hospital, Montreal, QC) from total hip replacement orthopedic surgeries. Patients signed consent forms for the donation of their tissue. All samples were wrapped in gauze and soaked in saline to prevent drying. The specimens were frozen at -30ºC until bone core extraction (14).

Prior to sample preparation, the femurs were thawed at 4ºC overnight. A Rochester Bone Biopsy Trephine (Item #87400-000, Gauthier Medical Inc., Rochester, MN) 7.5mm in diameter was used to extract cylindrical cores of trabecular bone from the centre of the femoral necks. Both ends of the cores were cut at right angles to the long axis in order to minimize shearing during biomechanical compression testing (15). The dimensions of the trabecular bone cores were 7.5mm in diameter by 14mm in length, thereby maintaining a valid aspect ratio between 1.5 and 2 (16). The cores were placed in 70% ethanol prior to testing (17).

The trabecular bone cores were scanned using a Lunar PIXImus densitometer (Lunar Corp, Madison, WI) at the Bone Centre (McGill University, Montreal, QC) to measure the bone mineral density (BMD) for a region of interest inside the specimen (11.3mm x 5mm). They were subsequently scanned with a micro-computed tomography (μCT) instrument (Model 1072, Skyscan, Aartselaar, Belgium) at the Bone Centre (McGill University, Montreal, QC). The cross-sections along the specimen axis were reconstructed using Cone-Beam Reconstruction software (SkyScan), with a distance between each cross-section of 18.25μm. The CT-Analyser software (SkyScan) was used to analyze the trabecular bone of the sample using segmentation method.

The bone cores were then subjected to the compression testing. Specimens were mounted on the testing machine (Instron 5569, Buckinghamshire, UK) so that the long axes of the cylinders were perpendicular to the lower anvil. A compressive force was then applied to the upper surface of the samples using a 50kN load cell at a constant crosshead displacement rate of 1 mm/min until failure occurred. The compressive load and the sample length were recorded at 0.1 second intervals during compression. Using this

data, the Stress (Force/Area) and Strain (Length/Original Length) were calculated and plotted against one another. The Elastic Modulus, an indication of the extent of compressive deformation in a specimen for a given load, was obtained from the linear portion of the Stress versus Strain curve (15).

RESULTS

Initially, it was imperative to demonstrate that the protocol used to retrieve cylindrical cores of cancellous bone would provide valid samples for biomechanical testing. Twenty two cores of cancellous bone were extracted from the femoral neck of calf femurs and subjected to compression testing. The compressive strength and the elastic modulus were calculated for each sample and plotted against each other. It should be noted that the compressive strength is a measure of the stress within a sample immediately before the yielding point, while the elastic modulus is a measure of the rigidity of a sample. In concordance with previous findings, the compressive strength correlates strongly to the modulus (r = 0.98) in the calf femur samples (see Figure 1) (18). Furthermore, these parameters fall within the range of published bovine values (19).

Upon validating our technique, the same procedure was applied to the human femoral neck samples obtained from hip replacement surgeries. Nineteen human samples were obtained and tested. Comparable to the bovine samples, the compressive strength and the modulus of the human samples are strongly correlated (r = 0.99), as demonstrated in Figure 2. Moreover, the values for these parameters fall within the range of published human values for the femoral neck (20).

Prior to subjecting the human cancellous samples to biomechanical testing, they were scanned using three dimensional μCT and densitometry. As demonstrated in Figure 3, the osteoporotic bone appears much more porous than the unaffected bone. The compressive strength was plotted against the trabecular thickness, number and separation, as shown in Figure 4. The latter parameters failed to show any statistically significant relationship to the biomechanics of bone. The trabecular thickness and separation remained fairly constant despite the strength of the bone, whereas the number of trabeculae appeared to increase with the compressive strength although not well. Needless to say, the trabecular data proved to be poor indicators of bone quality.

Further investigation of the imaging data revealed that the relative porosity, calculated as the complement of the percent bone volume (i.e. 1 - % bone volume), and the BMD were the best predictors of bone quality. In fact, the relative porosity and the BMD correlated strongly to one another (see Figure 5, r = 0.97). Upon analyzing the data, the compressive strength and the modulus were shown to vary exponentially with relative porosity and the BMD. That is to say, the strength and the modulus of the samples increased at a faster rate as the relative porosity decreased or the BMD increased. Thus, the latter were plotted against the natural logarithms of the compressive strength and the modulus for each bone sample (see Figures 6-9). The relative porosity and the BMD correlated equally well to the compressive strength and the modulus (Ln(compressive strength) vs. relative porosity, r = -0.90; Ln(modulus) vs. relative porosity, r = -0.88; Ln(compressive strength) vs. BMD, r = 0.94; Ln(modulus) vs. BMD, r = 0.92).

DISCUSSION

The assessment of bone quality is of the utmost importance in osteoporotic patients as it correlates well to the risk of fracture (1) and indicates when it is appropriate to initiate the proper preventative measures (6-8). Bisphosphonates have proven to be quite successful in deterring the progression of osteoporosis (6). However, their precise mechanism of action has yet to be determined. Recently, there have been trials that have studied the effect of risedronate in osteoporotic patients using μCT (11). These studies have indirectly assessed the drug's effect on bone quality using a remote site (i.e. the iliac crest) rather than the site of interest (e.g. vertebrae, femoral neck). Understandably, the analysis of the iliac crest is convenient because it is easily accessible from the surface and poses minimal risk to the patient. There has been, however, no evidence to indicate whether any correlation exists

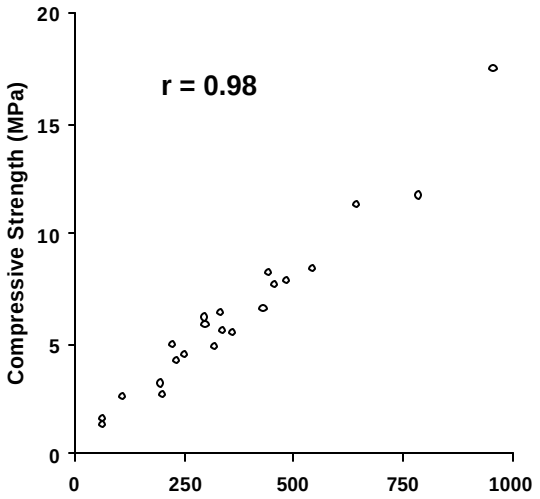

Figure 1: Compressive strength versus Modulus in cancellous bone from calf femoral necks. Both parameters are measured in MegaPascals (MPa). Correlation coefficient, r = 0.98

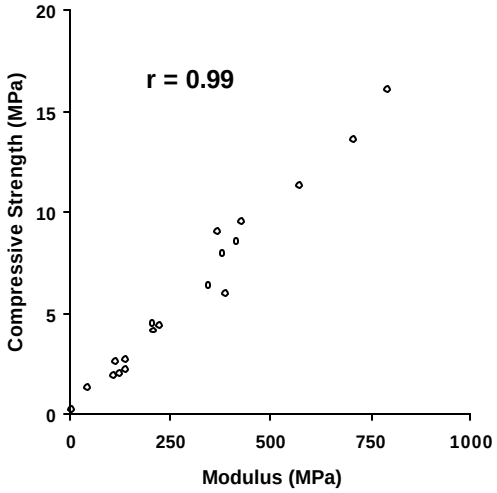

Figure 2: Compressive strength versus Modulus in cancellous bone from human femoral necks. Both parameters are measured in MegaPascals (MPa). Correlation coefficient, r = 0.99.

between the microarchitecture at the iliac crest and the site of interest. To our knowledge, the effects of bisphosphonates on bone quality have not yet been studied in humans at sites than at the iliac crest.

Prior to embarking on a hip fracture study, we wanted to establish reliable and reproducible procedures for biomechanical testing to ensure that the data were valid and representative of bone quality. Intuitively, bone quality should diminish as the bone becomes more porous and/or less dense with mineral. Indeed, we found the relative porosity and the BMD to be equally strong indicators of bone quality as both of these parameters correlate strongly to the biomechanical properties of bone, though in opposite fashion (see Figures 6-9).

A potential limitation to this experiment is the inherent design flaw that results from the extraction of trabecular bone. As the cylindrical core of bone is removed from the sample, the cross struts from the trabeculae along the periphery are severed. This unavoidably compromises structural integrity, especially since the compact bone significantly contributes to the overall strength of the femur (21). Hence, the biomechanical studies will not be entirely representative of the properties of trabeculae within the bone. However, taking into consideration that all the samples are prepared identically before testing, the data analysis remains valid.

CONCLUSION

We have successfully established a protocol that will be used in a trial setting to analyze the bone quality in human femoral necks using µCT and biomechanical compression testing. Using cores of cancellous bone from human femoral necks, the relative porosity and the BMD were shown to be excellent predictive markers of fracture resistance. As this trial evolves in its early stages, additional samples collected from hip replacements will be tested and the data compiled to construct a reference database for comparison to bisphosphonate treatment cohorts.

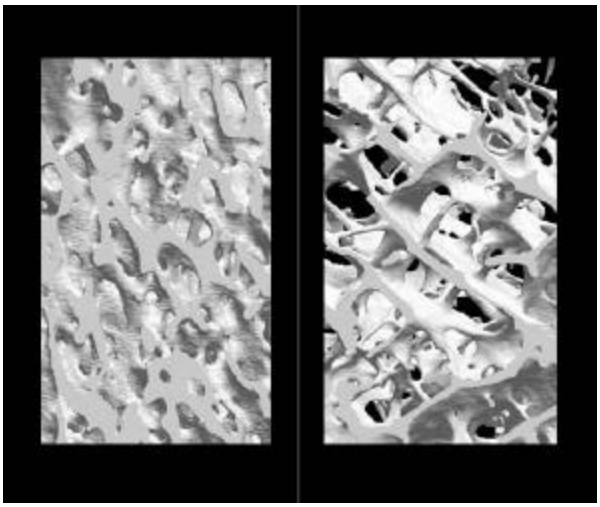

Figure 3: Computer-generated three dimensional images of unaffected bone (left panel) and osteoporotic bone (right panel) from µCT scans.

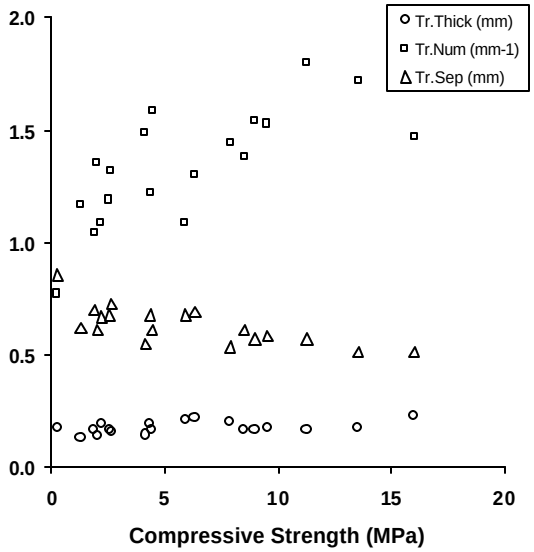

Figure 4: Trabecular thickness (Tr.Thick, circles), number (Tr.Num, squares), and separation (Tr.Sep, triangles) plotted against Compressive Strength in MegaPascals (MPa). Trabecular thickness and separation are measured in millimeters (mm) and trabecular number is measured as the quantity of trabeculae per millimeter (mm^{-1}).

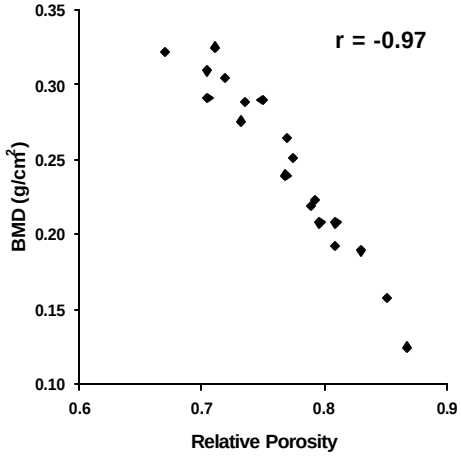

Figure 5: BMD plotted against Relative Porosity. Correlation coefficient, r = -0.97.

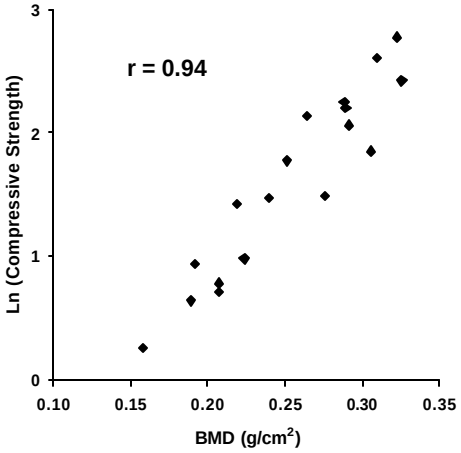

Figure 8: The natural logarithm of Compressive Strength plotted against BMD. Correlation coefficient, r = 0.94.

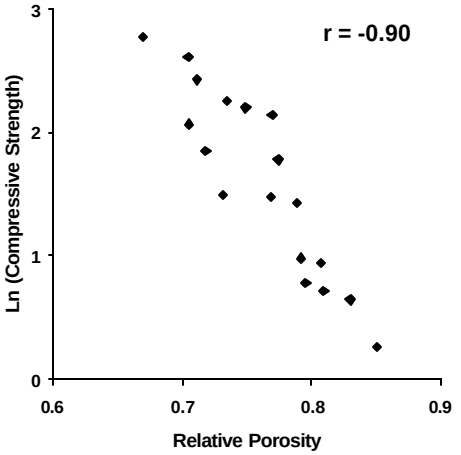

Figure 6: The natural logarithm of Compressive Strength plotted against Relative Porosity. Correlation coefficient, r = -0.90.

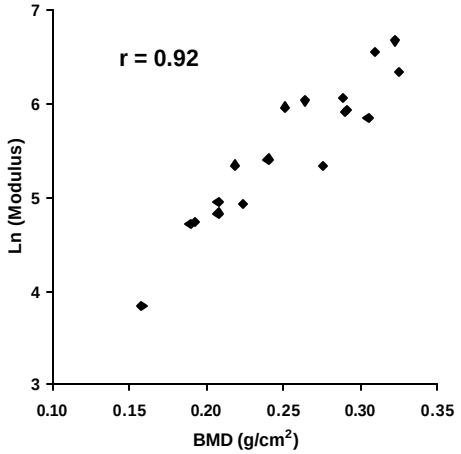

Figure 9: The natural logarithm of Modulus plotted against BMD. Correlation coefficient, r = 0.92.

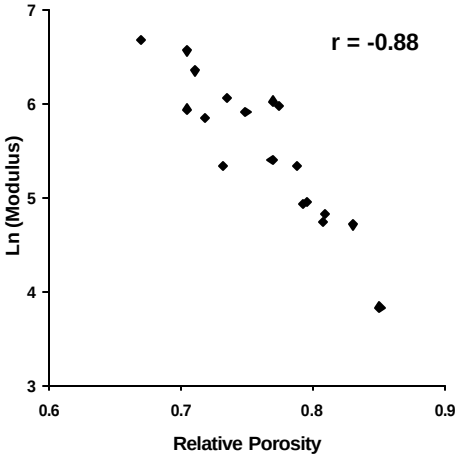

Figure 7: The natural logarithm of Modulus plotted against Relative Porosity. Correlation coefficient, r = -0.88.

REFERENCES

1. WHO, Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, in Report of a WHO study group. WHO technical report series no. 8430. 1994, World Health Organization: Geneva, Switzerland.
2. Boonen, S., et al., Preventing osteoporotic fractures with antiresorptive therapy: implications of microarchitectural changes. J Intern Med, 2004; 255(1): p. 1-12.
3. Seeman, E., Invited Review: Pathogenesis of osteoporosis. J Appl Physiol, 2003; 95(5): p. 2142-51.
4. Russell, R.G., et al., The pharmacology of bisphosphonates and new insights into their mechanisms of action. J Bone Miner Res, 1999; 14(Suppl 2): p. 53-65.
5. Manolagas, S.C., Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev, 2000; 21(2): p. 115-37.
6. Black, D.M., et al., Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.

Fracture Intervention Trial Research Group. Lancet, 1996; 348(9041): p. 1535-41.
7. Ensrud, K.E., et al., Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. Arch Intern Med, 1997; 157(22): p. 2617-24.
8. Harris, S.T., et al., Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Jama, 1999; 282(14): p. 1344-52.
9. Day, J.S., et al., Bisphosphonate treatment affects trabecular bone apparent modulus through micro-architecture rather than matrix properties. J Orthop Res, 2004; 22(3): p. 465-71.
10. Osteoporosis prevention, diagnosis, and therapy. Jama, 2001; 285(6): p. 785-95.
11. Borah, B., et al., Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. Bone, 2004; 34(4): p. 736-46.
12. Passi, N. and A. Gefen, Trabecular bone contributes to strength of the proximal femur under mediolateral impact in the avian. J Biomech Eng, 2005; 127(1): p. 198-203.
13. Rosenthall, L., J.D. Bobyn, and M. Tanzer, Bone densitometry: influence of prosthetic design and hydroxyapatite coating on regional adaptive bone remodeling. Int Orthop, 1999; 23(6): p. 325-9.
14. Panjabi, M.M., et al., Biomechanical time-tolerance of fresh cadaveric human spine specimens. J Orthop Res, 1985; 3(3): p. 292-300.
15. Currey, J.D., The mechanical properties of bone. Clin Orthop Relat Res, 1970; 73: p. 209-31.
16. Price, W., Factors influencing concrete strength. J Am Con Inst, 1995; 31: p. 417-33.
17. Linde, F. and H.C. Sorensen, The effect of different storage methods on the mechanical properties of trabecular bone. J Biomech, 1993; 26(10): p. 1249-52.
18. Hodgskinson, R. and J.D. Currey, Effects of structural variation on Young's modulus of non-human cancellous bone. Proc Inst Mech Eng (H), 1990; 204(1): p. 43-52.
19. Hodgskinson, R. and J.D. Currey, The effect of variation in structure on the Young's modulus of cancellous bone: a comparison of human and non-human material. Proc Inst Mech Eng (H), 1990; 204(2): p. 115-21.
20. Martens, M., et al., The mechanical characteristics of cancellous bone at the upper femoral region. J Biomech, 1983; 16(12): p. 971-83.
21. Lotz, J.C., E.J. Cheal, and W.C. Hayes, Stress distributions within the proximal femur during gait and falls: implications for osteoporotic fracture. Osteoporos Int, 1995; 5(4): p. 252-61.

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ORIGINAL ARTICLE

Encapsulated calcium carbonate suspensions: A drug delivery vehicle sensitive to ultrasound disruption

Brent Lanting*, Joe Barfett*

ABSTRACT: A calcium carbonate suspension, encapsulated within particles of calcium alginate hydrogel, is proposed as a drug delivery device susceptible to ultrasound disruption. Spheres approximately 1mm in diameter were prepared by the coaxial airflow method from mixtures of 1% sodium alginate (m/v) and each of 50%, 75% and 100% calcium carbonate (m/v) in distilled water. This product was subjected to cycles of 85 Watt ultrasound in 1 second on/off bursts via a lab sonication system until fully disintegrated, a process requiring between 8 and 20 minutes depending upon initial calcium carbonate concentrations. The spheres subjected to vortex did not demonstrate any signs of mechanical degeneration after 30 minutes. Before use as a model implant, further work is required to develop a method of drying the particles to make them impermeable to drug diffusion before the time of their disruption with ultrasound.

KEYWORDS: alginic acid, microencapsulation, controlled release, ultrasound

INTRODUCTION

Despite the general use and success of systemic therapies, there has always been an interest in maximizing drug availability in target tissues and minimizing adverse reactions. As a result, many simple, local, and highly effective drug treatments have been developed including drops for eyes and ears, puffers for the respiratory tract, sprays for the sinuses, creams for skin and mucosa, central nervous system shunts and other implants. Local therapy, where appropriate, allows maximum bioavailability in target tissues while minimizing systemic interactions and allowing for the lowering of drug dosages needed for therapeutic effectiveness.

Interest in the development of new drugs is therefore balanced by the increasing emphasis placed on novel delivery systems (1,2). Such technologies have been subject to intense development over the past decade and now occupy a multibillion dollar per annum industry in the United States (1). In particular, polymers capable of controlled pharmaceutical release are of significant interest and offer to expand the range of diseases amenable to more localized treatment. The most classic systems rely upon temperature, pH, magnetic fields, light, mechanical force, or ultrasound (as in the presently described system) to cause a change that facilitates drug release by diffusion (3,4,5,6). Such "smart polymers" often work well in vitro but demonstrate severe limitations when constrained to more physiological conditions.

As a simple alternative, we propose a drug delivery vehicle based upon calcium carbonate powder suspended in particles of a calcium alginate hydrogel matrix. Alginate hydrogels are soft and non-toxic polymers traditionally used as food thickeners, but have more recently found applications in both industrial and

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medical encapsulation technologies for controlled release (7). Calcium carbonate powder is insoluble, non-toxic, and known to be susceptible to ultrasound (8). The combination of these two inexpensive materials produces a medically useful hydrogel matrix that can be disintegrated with high intensity sound waves. So far as the authors are aware, this is the first attempt to combine these materials for the purposes of creating an ultrasound activated drug delivery device.

METHODS

A co-axial airflow encapsulation nozzle was constructed as described by Fiszman et al (7). The authors varied the flow rates described below until macroscopic particles of desirable diameter were attained. It was thought that a 1mm spherical diameter offered balance between a small enough object to theoretically inject and yet large enough to work with on a macroscopic scale.

Briefly, a 16 gauge needle, connected to a peristaltic pump via lab tubing, was passed through a ¼ inch "T" junction and secured in place, thus plugging one of the T's three ports. To the horizontal inlet was attached an air hose and pump such that air could be forced around the 90 degree bend and over the needle tip. Via a procedure modified from Yang (9), a 1% (m/v) algin solution was prepared by dissolving 1000.0 mg of sodium alginate (Sigma) in 100.0cc of distilled water with intense agitation via vortex for 30min. Preparations were made including 50g, 75g and 100g of calcium carbonate (Sigma) in the sodium alginate solution to create final 50%, 75% and 100% (m/v) mixtures.

Suspension was forced through the needle by a peristaltic pump at a rate of 8cc/min while air flowed around the tip at 4L/min, creating enough shear force to convert the liquid stream into fine droplets. These fell 10cm into a 4% (m/v) $CaCl_2 \cdot 2H_20$ hardening solution below. Four hours were allowed for full polymerization of the particles before they were spun out of solution by gentle centrifugation and re-suspended in normal saline after three washes. Spheres produced by the above method measured approximately 1mm in diameter and were of an opaque white color.

Three particles of each final calcium carbonate concentration were separated into each of three plastic centrifuge tubes and used for the sonication trials. The tubes were subjected to bursts of ultrasound at 85 watts, one second on and one second off, until fully disintegrated. The time required for full disintegration was recorded. Similarly, an identical set of three tubes, three alginate spheres per tube, were agitated by vortex for a period of twenty minutes to gain a rough assessment of the product's mechanical stability without the use of ultrasound disruption.

RESULTS

Table 1. Calcium Carbonate Concentrations in 1% Algin Related to Time to Total Disruption with 85 Watt Ultrasound in 1 Second Bursts

	Trial One	Trial Two	Trial Three
50% $CaCO_3$	16:34	19:43	19:22
75% $CaCO_3$	11:45	15:55	16:22
100% $CaCO_3$	8:45	12:10	9:12

Using the same parameters of three particles per plastic tube and 85 Watt ultrasound bursts of 1 second on/off, the time necessary to disintegrate the particles was found as a function of calcium carbonate concentration in the initial encapsulation mixture (see Table 1). Three trials at each concentration were used. Disintegration of the spheres was determined qualitatively by viewing the attained product under a microscope.

Table 2. Spheres Subjected to Agitation Via Vortex

	Trial One	Trial Two	Trial Three
50% $CaCO_3$	>30 min	>30 min	>30 min
75% $CaCO_3$	>30 min	>30 min	>30 min
100% $CaCO_3$	>30 min	>30 min	>30 min

Similarly, three spheres of each of the three calcium carbonate concentrations were subjected to three trials of agitation by vortex. In each case, no signs of particle disintegration could be observed after thirty minutes (see Table 2).

DISCUSSION

It is clear that an increasing concentration of calcium carbonate leads to a decrease in the time necessary for particle disintegration. Increasing the concentration of calcium carbonate both raises the amount of material in each sphere sensitive to ultrasound and reduces the relative concentration of alginate. As such there becomes less alginate hydrogel to hold particles together. We experimented with a range of values before running final trials at 50%, 75% and 100% calcium carbonate. Using calcium carbonate concentrations of less than 50% drastically increased the time necessary for ultrasound disruption, while concentrations greater than 100% increased viscosity of the mixture and made extrusion through the needle very difficult.

Time-dependent diffusion of substances through an alginate matrix has been previously demonstrated, with diffusion times varying over minutes to hours depending upon the weight of the molecule in question and the initial concentration of sodium alginate used to make an encapsulation polymer (10). While we may reasonably conjecture that the particles generated in this study would share diffusion characteristics with those published, our initial goal was to dry particles in order to create a hard external calcium carbonate diffusion barrier. Drying particles in an incubator, however, generated a product that adhered too firmly to the drying surface to be removed without damage. A number of drying surfaces were attempted without success.

Limitations of this study include the lack of a quantitative method to determine the rate of sphere disintegration as a function of the number of ultrasound bursts to which they were subjected. Second, a method to quantify the amount of agitation delivered would be helpful so that the maximum mechanical disruption tolerated by spheres can be identified. Finally, although the coaxial airflow technique described in this study is a simple and widely used system of generating even micro-scale hydrogel particles, we found the reproducibility of particle shape and size to be limited from batch to batch. There are techniques available which offer greater reproducibility of product and smaller sphere size, albeit at much greater cost (11).

CONCLUSION

We have demonstrated a process by which routinely available and non-toxic materials can be used to create particles of encapsulated calcium carbonate in a calcium alginate hydrogel. The resulting product is easily disrupted with ultrasound and yet retains structural integrity under agitation by vortex for an extended period. There are logical implications for these particles to be injected into a target tissue under image guidance and subsequently identified via fluoroscopy or CT scan. Destruction of particles with therapeutic ultrasound and the controlled release of encapsulated drugs is a reasonable future experimental goal.

Our next set of experiments will involve a system to dry spheres while they are simultaneously agitated. It will thus be possible to quantify the diffusion characteristics and parameters of ultrasound disruption on dried particles. We are also working with microscopes that can photograph particles, the disruption products, as well as potentially measure the reduction of particle radius as a function of ultrasound delivery.

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REFERENCES

1. Richard A, Margaritis A. Production and Mass Transfer Characteristics of Non-Newtonian Biopolymers for Biomedical Applications. Critical Reviews in Biotechnology 22(4): 355-374; 2002.
2. Chemical Market Reporter, Drug Delivery Market Poised for Five Years of Strong Growth. Schnell Publishing, New York, 258(23); 2000.
3. Sershen S, West J. Implantable Polymeric Systems for Modulated Drug Delivery. Advanced Drug Delivery Reviews 54:1225-1235; 2002.
4. Kost J, Wolfrum J, Langer R. Magnetically Enhanced Insulin Release in Diabetic Rats. Journal of Biomedical Materials Research 21: 1367-1373; 1987.
5. Kwok C, Mourad PD, Crum LA, Ratner BD. Self-Assembled Molecular Structures as Ultrasonically-Responsive Barrier Membranes for Pulsatile Drug Delivery. Journal of Biomedical Materials Research 57(2): 151-164; 2001.
6. Dinarvand R, D'Emanuele A. The Use of Thermoresponsive Hydrogels for On-Off Release of Molecules. Journal of Controlled Release 36: 221-227; 1995.
7. Fiszman GL, Karara, AL, Finocchiaro, LME, Glikin GC. A Laboratory Device for Microencapsulation of Genetically Engineered Cells into Alginate Beads. Electronic Journal of Biotechnology 5(3); 2002.
8. Mitri FG, Fellah ZEA, Closset E, Trompette P, Chapelon JY. Determination of Object Resonances by Vibro-Acoustography and their Associated Modes. Ultrasonics 42(1-9): 537-543; 2004.
9. Yang H, Wright JR. Calcium Alginate. In: Kuhtreiber WM, Lanza RP, Chick WL. Cell Encapsulation Technology and Therapeutics. Berlin, Germany: Birkhauser Publishing, 1999.
10. Millman JS. Diffusivity Characteristics of Globular Proteins in Calcium Alginate Immobilization Matrices. Faculty of Graduate Studies, University of Western Ontario, London, ON, 1992.
11. Dulieu C, Poncelet D, Neufeld R. Encapsulation and Immobilization Techniques. In: Goosen MFA, editor. Fundamentals of Animal Cell Encapsulation. Anne Arbor, MI: CRC Press, 1993.

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ORIGINAL ARTICLE

Sexual assault and posttraumatic stress disorder: A review of the biological, psychological and sociological factors and treatments

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ABSTRACT: Sexual assault occurs with alarming frequency in Canada. The prevalence of Posttraumatic Stress Disorder (PTSD) in assault survivors is drastically higher than the national prevalence of the disorder, which is a strong indication that the current therapies for sexual-assault-related PTSD are in need of improvement. Increasing knowledge and understanding of the pathologies associated with rape trauma in biological, psychological and sociological domains will help to develop more effective treatments for survivors. A dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis is observed in survivors of sexual assault and this may be a fundamental cause of the structural and functional abnormalities contributing to PTSD symptoms. Pharmacotherapies are available to treat PTSD; however, they are often inadequate or unwanted by the survivor. Psychological health is compromised following interpersonal trauma and many psychological therapies are available, but with varying efficacy. A person's cognitions have a dramatic effect on the onset, severity, and progress of PTSD following sexual assault. Sociological impacts of assault influence the development of PTSD through victim-blaming attitudes and the perpetuation of rape myths. Perceived positive regard and early social support is shown to be important to successful recovery. Education is vital in rape prevention and to foster a supportive environment for survivors. The biological, psychological and sociological impacts and treatments should not remain mutually exclusive. A better appreciation of the biopsychosocial repercussions of sexual assault will aid in developing a more holistic and individualized therapy to help alleviate the physical and emotional pain following the trauma of rape.

KEYWORDS: posttraumatic stress disorder, trauma, sexual assault, rape, pharmacotherapy.

INTRODUCTION

One woman is sexually assaulted in Canada every minute (1). Sexual assault is any form of sexual contact without voluntary consent andthat violates a person's sense of autonomy, control and mastery over their body (2). At the University of Alberta, 21% of students have reported at least one unwanted sexual experience (3). Sexual assault is widespread and occurs with alarming frequency.

Recovery from sexual- assault- related Posttraumatic Stress Disorder (PTSD) is not solely measured by eliminating symptoms or achieving specific outcomes. Healing from this trauma does not mean that the survivor will forget the experience or never again experience any symptoms. Rather, successful recovery is subjective and measured by whether the survivor

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increases his or her involvement in the present, acquires skills and attitudes to regain control of his of her life, forgive him or herself for guilt, shame and other negative cognitions, and gain stress reduction skills for overall better functioning (4). There are many factors involved in successful recovery, including the degree of support received, previous self-concept, personal strength, and professional treatment provided by the medical and justice systems (5). PTSD is one of the problems that may result from failure of the recovery process.

PTSD is caused by exposure to a traumatic event and intense psychological distress occurs as a result of re-experiencing the event (6). PTSD is diagnosed when symptoms last longer than one month (7). To prevent the distressing reactions, survivors will avoid stimuli that provoke these feelings and this avoidance behaviour can be severe enough to significantly impair daily life (8).

The consequences of a sexual assault may be manifested biologically, psychologically, and sociologically. By gaining a better appreciation of the repercussions of sexual assault, a holistic and individualized therapy can be developed to ameliorate the physical and emotional pain following the trauma. The issues facing individuals who have experienced sexual assault will be discussed and improvements in current treatments will be suggested, with hopes to develop more effective and holistic therapies in the future.

POSTTRAUMATIC STRESS DISORDER

The US National Comorbidity Survey Report estimates the lifetime prevalence of PTSD among North Americans to be 7.8% (9). The lifetime prevalence of PTSD for women who have been sexually assaulted is 50% (10). Moreover, sexual assault is the most frequent cause of PTSD in women, with one study reporting that 94% of women experienced PTSD symptoms during the first two weeks after an assault (9).

The alarmingly high rate of PTSD in survivors of sexual assault is a strong indication that the current therapies for rape victims are inadequate and in need of improvement. There is no 'cookie cutter' treatment for every victim suffering with PTSD, as the disorder can manifest itself in many ways (8). It is important to consider the biological, psychological, and sociological impacts when developing effective treatment and intervention methods for sexual-assault-related PTSD.

PTSD PATHOPHYSIOLOGY

Before treatment for sexual-assault-related PTSD can be developed, an understanding of the pathophysiology of PTSD is critical. The dysregulation seen in individuals with PTSD can be observed and measured on all major systems of the body including the neural, endocrine and immune systems (6). The Hypothalamic-Pituitary-Adrenal (HPA) axis plays a key regulatory function in the body, controlling all three systems through negative feedback inhibition. Cortisol is a major hormone of the HPA axis and is the primary stress hormone in the body. It is released when stimulated by Corticotropin Releasing Hormone (CRH) and inhibited via negative feedback acting at the hypothalamic and pituitary levels. Intense psychological trauma such as sexual abuse can cause changes in the body's response to stress by increasing levels of CRH and dysregulating the HPA axis (11, 12). This results in a decreased number of CRH receptors in the anterior pituitary, decreased pituitary responsiveness to CRH, and disturbed negative feedback inhibition (13). Reduced responsiveness to CRH causes overactivation of the HPA axis and can disturb negative feedback by cortisol (Figure 1). Cortisol has widespread action and its dysregulation affects other neural systems including the mesocorticolimbic dopaminergic system, leading to inappropriate fear reactions and persistent mild depression (14).

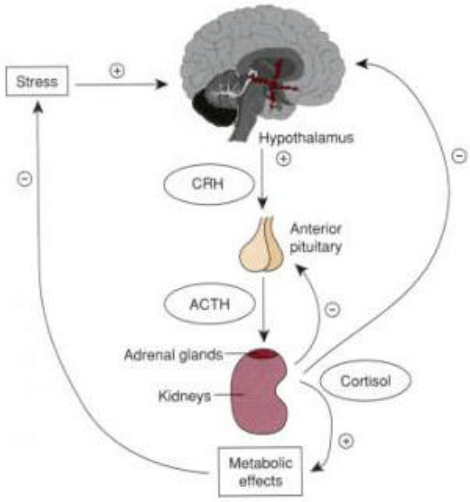

Figure 1. The hypothalamic-pituitary-adrenal axis
The HPA axis is dysregulated in survivors of sexual assault. A reduced responsiveness to CRH is observed and the negative feedback by cortisol on the hypothalamus and pituitary is disturbed.

[Retrieved April 9th, 2006 from http://www.montana.edu/wwwai/imsd/alcohol/Vanessa/vwhpa_files/image003.jpg]

PHARMACOTHERAPY TREATMENT OPTIONS FOR PTSD

Knowledge of the biological changes with PTSD has led to the development of new treatments that offer more comprehensive management of PTSD and enable patients to enjoy an improved quality of life (11). For

example, various drug treatments have been developed to treat PTSD. There are five main goals for treating PTSD with medications, including a reduction of the core symptoms such as anxiety and flashbacks, an improvement in stress resilience, an improvement in the quality of life, and a reduction in disability and comorbidity (15). As Brunello et al. notes, it is important to maintain wellness and prevent relapse (6).

Concurrent with HPA axis dysfunction, disruption of glutamatergic, serotonergic, and adrenergic systems is a fundamental cause of the structural and functional abnormalities which contribute to the symptoms of PTSD. Such symptoms include hyperarousal and re-experiencing feelings associated with the trauma through flashbacks or nightmares (11). The persistent re-experiencing of traumatic events may cause an increase in CRH levels, which damages the hippocampus, an important region of the brain associated with learning and memory (16, 17). With psychological trauma, a decrease in hippocampal volume has been observed (6). This volume decrease, when coupled with hypersensitivity of the HPA axis, is associated with a reduction of cognitive functioning drastically affecting the performance of affected individuals (18). Selective Serotonin Reuptake Inhibitors (SSRIs) have been successfully used to treat these hyperarousal symptoms purported to be caused by a decrease in hippocampal volume. SSRIs are commonly used to treat depression and there is some evidence that they may promote neurogenesis, which might be the therapeutic mechanism by which these medications effect changes in behaviour (18). For example, Bremner and Vermetten demonstrated a 4.6% increase in the volume of the hippocampus and an improvement in memory of PTSD patients through treatment with the SSRI Paroxetine (18).

Many hormones and receptors in the glutamatergic, serotonergic, and adrenergic systems have been identified as key factors in memory and perception, one of which is the gamma-aminobutyric acid receptor (GABA-R) (11). Following sexual abuse and the development of PTSD, the dysregulation of the HPA axis can stimulate the adrenergic system, activating GABA-R (15). The multifaceted interactions between these systems may explain the connections of emotions with factual memory. It has been proposed that while a traumatic memory is re-lived during a flashback, there is an increase in the stimulation of GABA-R caused by an increase in the release of endogenous benzodiazepines (15). To control the overstimulation of GABA-R and thereby control anxiety and flashbacks, benzodiazepine inhibitors such as flumazenil have been used successfully (11). This has also been achieved with clonidine to stop nightmares by decreasing the release of catecholamines, a key component of the anxiety-provoking 'fight or flight' response of the autonomic nervous system (19).

The immune system is reciprocally regulated by the neural and endocrine systems and can also be affected by PTSD (20). PTSD often co-occurs with various inflammatory diseases, likely due to HPA axis dysregulation affecting the immune system (21). Immunomodulation is therefore important to avoid this subsequent dysregulation of the immune system and this can be achieved with SSRIs such as Fluvoxamine.

Fluvoxamine has been shown to be effective in decreasing the hyperresponsiveness of the HPA axis, thereby increasing levels of interleukins and other essential immune factors (22). Interestingly, there is a sexual dimorphism in immune functioning, as men with PTSD were found to have an inhibited cell-mediated immunity, while women showed enhanced cell-mediated immunity (21). A better understanding of this is necessary and it is important to consider sexual dimorphism for immunomodulation.

Other drug treatment options are available for PTSD including Tricyclic Antidepressants (TCA), Monoamine Oxidase Inhibitors (MAOI), SSRIs, serotonin antagonists, and anticonvulsants and are described in Table 1 (23). Although there are some promising studies for medications, reviews of pharmacotherapies for PTSD have revealed that most treatments are inadequate, aside from some supportive evidence of SSRI effectiveness (24). Therefore it is useful to look towards other disciplines for additional treatment.

PSYCHOLOGY OF PTSD AND COGNITIVE FACTORS

Although the pathology associated with PTSD has a biological basis, the treatment need not be restricted to drugs. For example, a serious consequence of HPA axis dysregulation is the effect on the steroid hormones, namely estrogen and testosterone, which are also modulated through this axis (25). As a result, some survivors of sexual assault can become infertile due to sex steroid dysregulation. Interestingly, research indicates that fertility may be restored with cognitive behavioural therapy (CBT), just one example of many where psychological intervention was used to treat a biologically based malady (26).

After an assault, survivors experience The Rape Trauma Syndrome (RTS), which affects not only victims of rape, but also victims of all types of sexual violence and would perhaps be better labelled as Sexual Assault Trauma Syndrome. RTS is characterized by three phases (27). The Acute Phase occurs immediately following the assault when the survivor is in crisis and experiences a wide range of emotional reactions. These

reactions may be categorized as Expressive, such as shaking, crying or yelling; or Controlled such as flattened affect, appearing outwardly calm and subdued. The second phase is Outward Adjustment, when the survivor focuses less on the assault, often with a high level of denial, and involves themselves in normal daily activities. The final phase is Long Term Reorganization, in which the survivor integrates the assault into their view of themselves and resolves their feelings about the assailant. There are many psychological effects to consider following a sexual assault such as feelings of shame, guilt, anxiety or depression (9). These feelings may be even stronger and more harmful if the survivor does not receive support from their family, friends or authorities (9).

Cognitive factors play a large role in the onset, severity, and outcome of PTSD after sexual assault (28). These factors include mental defeat and confusion,

Table 1. Summary of pharmacologic treatment options for PTSD

Drug classification	Drug Name	Effects on PTSD improvement
Tricyclic antidepressants	Amitryptiline	- 50% of treated patients had a final CGI-I[1] score of 1 or 2 ("very much" or "much improved") as compared to 17% for placebo
	Imipramine	- 25% decrease from baseline in IES[2] scores for treated patients as compared to 5% for placebo - 65% of treated patients were found to improve on a Global Scale as compared to 28% for placebo
Monoamine Oxidase Inhibitors	Phenelzine	- 45% decrease from baseline in IES score as compared to 5% for placebo
	Brofaromine	- Reductions in PTSD symptoms were reported, however no difference was found between treatment group and placebo group
	Moclobemide	- 11 of 20 participants no longer met the criteria for PTSD at the end of a 12 week trial
Selective Serotonin Reuptake Inhibitors	Fluoxetine	- 85% of treated patients showed improvement on a Global Rating Scale as compared to 62% of patients taking placebo - Response rate on High End State Functioning was 41% for treatment group and 4% for placebo
	Sertraline	- 43% decrease in CAPS[3] score for treatment group as compared to 31% for placebo - 39% decrease in DTS[4] score for treatment group as compared to 24% for placebo
	Paroxetine	- 50% decrease in DTS score for treatment group - 40% decrease in IES score for treatment group
	Fluvoxamine	- 64% of patients had a Duke Improvement score or 1 or 2 - Significant reductions in mean scores for all efficacy scales used (TOP-8[5], DTS, IES)
5-HT2 Antagonist	Nefazodone	- A decrease in PTSD severity on a Primary Assessment Scale in both combat veterans and civilians was observed
Anticonvulsants	Lamotrigine	- 50% of patients in treatment group responded as compared to 25% for placebo group*
	Carbamazepine	- 70% of patients had a response of "moderate" or "very much" improvement
	Valproate	- Approximately 70% of patients had a response of "moderate" or "very much" improvement

1. Clinical Global Impressions-Improvement Scale
2. Impact of Events Scale
3. Clinician Administered PTSD Scale
4. Davidson Trauma Scale
5. 8-Item Treatment-Outcome PTSD Scale

negative appraisal of emotions and symptoms, avoidance and perceived negative responses from others (5). If the survivor of sexual assault believes that others have failed to react in a positive and supportive manner, there is a greater risk of PTSD (9). It has been suggested that trauma recovery is characterized by a reprogramming, integration, and habituation to the traumatic images, leading to a restoration of a sense of safety (29). Over time, PTSD symptoms will decrease, the survivor will be less preoccupied with blame towards self and others, and a will achieve a regained sense of control (29).

Events perceived as uncontrollable are much more distressing than controllable events, therefore with uncontrollable events such as sexual assault, survivors will attempt to attribute blame to behavioural, dispositional or vicarious causes (30). Behavioural self-blame has the potential to be adaptive as it promotes the belief that negative outcomes can be avoided in the future; whereas dispositional self-blame attributes the traumatic event to one's personality and this thinking does not give a sense of future control (30). Vicarious control refers to the perception that some other person or entity had control over the occurrence of that event (30). Attributing blame in any of these ways focuses on the past and is associated with poorer outcomes in PTSD. To improve PTSD, treatment outcomes emphasis should be on controlling the present situation and what can be done about the impact of the event, rather than how it could have been avoided or can be avoided in the future (30). In view of the fact that control over the recovery process results in lowered distress levels, fostering this form of control could be an important component of interventions for sexual assault survivors (30).

Early intervention is critical for sexual assault victims because the level of distress immediately following the assault is strongly correlated to future pathologies and PTSD (31). In a study collecting self-reports from survivors of assault that assessed their degree of support and psychological distress during and immediately following the rape, it was found that high distress levels significantly predicted increased levels of fear and anxiety in the months following the assault (31). As the level of distress is strongly correlated to PTSD symptoms, an attempt to decrease levels of distress immediately following sexual assault may result in a more positive treatment outcome. When survivors seek medical assistance, the forensic rape exam can be very traumatizing (32). Resnick et al., demonstrated that meeting with a rape crisis counsellor or viewing a video before a forensic rape exam depicting in detail what to expect during the exam, resulted in decreased levels of stress after the exam in test groups compared to the non-video control group (32). Of all the eligible women, 81% agreed to participate in this video study, indicating that this is a feasible way to decrease distress and reduce future PTSD development following the physical examination.

Since November 1999, the Edmonton Capital Health Authority has run the Sexual Assault Response Team of Edmonton (SARTE) (33). This form of intervention has been very effective in lowering levels of distress in the hospital setting. SARTE consists of a team of nurses who are sensitized to the particular needs of survivors, and specialized in dealing with victims of sexual assault. When working with survivors, the nurses explain in detail the procedures they will perform, assist patients in reporting to the police, and maintaining an open environment where the survivor is able to make as many decisions on their own as possible (28).

PSYCHOTHERAPY TREATMENT OPTIONS FOR PTSD

In addition to promising social programs, there are many therapies focussing on the psychological aspect of PTSD. CBT focuses on changing thought patterns and cognitions to decrease negative emotions, develop skills to cope with anxiety and negative thoughts, restore effective social skills, and develop ways to manage anger and future trauma symptoms (9).

Eye Movement Desensitization and Reprocessing (EMDR) is an Information Processing Therapy that combines elements of CBT, psychodynamic, interpersonal, experiential and body-centred therapies to treat PTSD (34). During EMDR, the client thinks of past or present traumatic experiences while concurrently focusing on a stimulus such as auditory tones, tactile stimulation, or visual cues (34). This leads to dual attention, changing the processing of the traumatic memories and decreasing anxiety when thinking about the traumatic experience. It has been suggested that PTSD is due to an inability to adequately process the trauma and EMDR may be useful in this reprocessing (35). In an EMDR study by Rothbaum, only 10% of participants who were treated with EMDR therapy exhibited PTSD symptoms after treatment, compared to 88% of non-treatment control patients (36). Although the role of the eye movements has been contested, EMDR is proving to be an effective treatment option for PTSD (36).

Group therapy can be very effective to help survivors focus on the present and share experiences with others in a safe and empathetic environment. According to one survey, over half of the women who experienced sexual assault within the previous five years never told anyone about their trauma (37). This silence can have an important impact on the development of PTSD, as the

degree of support received can influence symptom severity (5). Individuals who receive bad or no support report more PTSD symptoms (28).

Psychodynamic therapy focuses on the emotional conflicts caused by the trauma, especially as they pertain to early life experiences. This helps to develop self-esteem, effective ways of thinking and coping, and may be used to treat PTSD (9). As discussed earlier, focusing on the past is associated with poorer adjustment and present control should be encouraged (30). As such, psychodynamic therapy may be less effective than other therapies for assault victims.

New psychological therapies and treatments are continually developed as older ones are re-evaluated. For example, trauma debriefing is common practice to reduce distress and aid in recovery immediately following a traumatic experience. Recently, it has been found that debriefing did not prevent the onset of PTSD and may even increase the risk of PTSD symptoms, demonstrating that treatments should be continuously evaluated and modified (38).

Both pharmacotherapy and CBT are viable treatment options for PTSD, however it is clear that empowering victims by giving back control is crucial in successful recovery. In one study, survivors were asked to choose between CBT with prolonged exposure to traumatic stimuli or the SSRI medication Sertraline (39). Participants of the study rated CBT as more credible and had more positive feelings towards this treatment option, citing effectiveness and potential side effects as the two primary factors in their decision. When presenting treatment options, it is important to explain both options and put side effects in perspective. Many women do not want pharmacotherapy and the therapy provider should give victims of assault a choice when deciding treatment options, to help them regain a sense of control (39).

SOCIOLOGICAL ISSUES CONTRIBUTING TO PTSD

Recovery from psychological issues due to sexual assault related PTSD is not solely an individual challenge, but also a challenge for those close to the affected individual (27). The recovery process is also a sociological issue and societal aspects should not be ignored. Research indicates that initial levels of distress and perceived control are key factors in the onset and severity of PTSD (31). Perceived positive regard and support has also been shown to be important to recovery (28). Less than half of individuals who have been sexually assaulted disclose the assault to others and it is clear that many are not getting the support they require. As a large part of the recovery process is related to a solid support network, part of the discussion of treatment and prevention of PTSD should be sociologically directed by targeting attitudes towards and origins of sexual assault with considerations of how these attitudes may create a rape-prone society and allow for such a high frequency of sexual assault.

There are many rape myths in our society, for example, beliefs that individuals lie about being assaulted, perpetrators are easily identifiable, or that men cannot be sexually assaulted. These myths promote negative attitudes and victim-blaming philosophies. Education is the first step in preventing PTSD associated with assault. The number of sexual assault victims willing to tell someone about their experience is increasing, potentially because there is less of a stigma attached to it today and there are more voluntary and professional support agencies (37). Although this shows some improvement, many individuals still have attitudes that sex role stereotyping, adversarial sexual beliefs, and acceptance of interpersonal violence, all of which lead to greater acceptance of rape myths (40). Although sexual assault programs are becoming more pervasive across college campuses, these programs are not always effective in implementing meaningful changes in cognition and behaviour (32). By understanding the failures of education programs, directions for improvement are found. Increasing program length may allow for more meaningful changes in cognition and behaviours to occur (41). Targeting the attitudes that lead to greater acceptance of rape myths may lead to a more supportive community for victims of sexual assault. Education is vital in rape prevention and to foster a supportive environment for survivors of this crime, but it is clear that more research is needed to improve the efficacy of these programs.

Many survivors who disclose their assault to others experience secondary victimization. Secondary trauma occurs when survivors seek assistance from medical, legal or healthcare professionals, but these professionals often exhibit and use victim-blaming behaviours (42). Contact with many services especially those which do not specialize in sexual assault traumatization, can increase survivors' psychological and physical distress (43).

Society contributes to the acceptance of rape myths through individuals the survivor solicits for help as well as by contributing to the negative cognitions of the survivors themselves. Negative cognitions foster self-blame and increase the risk of post-assault psychopathologies, likely contributing to the low disclosure rates.

CONCLUSION

Recovery from rape trauma is a deeply personal and

highly individualized journey. As knowledge of the pathophysiology of PTSD improves, more effective medications are developed to treat and manage the biological aspects of this disorder. Psychological therapies are available to assist survivors in their recovery. The number of rape prevention centres and education programs are on the rise with aims to debunk rape myths, change victim-blaming attitudes and de-stigmatize the subject. One of the most important aspects in assisting the recovery process is empowering the survivor and putting control back into their hands. The three-treatment modalities for the biological, psychological, and sociological impacts should not remain mutually exclusive. Physicians, therapists, law enforcement agencies, and family and friends must work together to find the meaning of recovery from the perspective of the survivors and to understand what conditions will facilitate growth and recovery. When the therapies available to treat sexual-assault-related PTSD are brought together during the right stages in the recovery process to form a comprehensive treatment of the highly individual survivor, greater success in decreasing the rate of PTSD associated with sexual assault may be achieved.

REFERENCES

1. Canadian Federation of Students. No Means No - Facts about Date Rape/Drug Rape. Canadian Federation of Students 1999 Fact Sheet, 6(2) Retrieved March 26, 2005, from http://www.cfs-fcee.ca/html/english/research/factsheets/fs-6(2)-nmn.pdf; 1999.
2. Rose, DS. Worse than Death: Psychodynamics of Rape Victims and the Need for Psychotherapy. The American Journal of Psychiatry 1986; 43(7): 817-824.
3. LoVerso, T. Survey of Unwanted Sexual Experience among University of Alberta Students. Retrieved March 26, 2005 from http://www.uofaweb.ualberta.ca/sac/nav01.cfm?nav01=27459; 2001.
4. Matsakis, A. I Can't Get Over It: Handbook for Trauma Aurvivors. Oakland, California: New Harbinger Publications; 1996.
5. Dunmore E, Clark DM, Ehlers A. Cognitive Factors Involved in the Onset and Maintenance of Post Traumatic Stress Disorder (PTSD) after Physical or Sexual Assault. Behaviour Research and Therapy 1999; 37: 809-829.
6. Brunello N, Davidson JRT, Deahl M, Kessler RC, Mendlewicz J, Racagni G et al. Posttraumatic Stress Disorder: Diagnosis and Epidemiology, Comorbidity and Social Consequences, Biology and Treatment. Neuropsychobiology 2001; 43: 150-162.
7. Butcher JN, Mineka S, Hooley JM. Abnormal Psychology 12th Edition. Boston, MA: Allyn and Bacon; 2004.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed., rev.). Washington, DC: American Psychiatric Association; 2000.
9. National Center for Post Traumatic Stress Disorder. Epidemiological Facts About PTSD - A National Center for PTSD Fact Sheet. Retrieved April 1, 2005 from http://www.ncptsd.va.gov/facts/general/fs_epidemiological.html; 2005.
10. Creamer M, Burgess P, McFarlane AC. Post-traumatic stress disorder: Findings from the Australian National Survey of Mental Health and Well-being. Psychol. Med 2001; 31(7): 1237-1247.
11. Nutt JD. The Psychobiology of Post Traumatic Stress Disorder. J Clin Psychiatry 2000; 61(5): 24-29.
12. Gold PW, Goodwin FK, Chrousos GP. Clinical and Biochemical Manifestations of Depression: Relation to the Neurobiology of Stress, Part II. N Engl J Med 319: 412-420; 1988.
13. Tizabi Y, Aguilera G, Gilad GM. Age Related Reduction in Pituitary Corticotrophin Releasing Hormone Receptors in Two Rat Strains. Neurobiol Aging 1992; 13: 227-230.
14. Perry BD, Pollard RA, Blakley TL, Baker WL, Vigilante D. Development of the Brain: How States Become Traits. Infant Mental Health Journal, July 25. Retrieved December 8, 2005 from http://www.trauma-pages.com/perry96.htm; 1995.
15. Davidson J, Glover V, Clow A, Kudler H, Meador K, & Sandler M. Tribulin in Posttraumatic Stress Disorder. Psychol Med 1988; 18(4): 833-836.
16. VanVoorhees E, Scarpa A. The Effects of Child Maltreatment on the Hypothalamic-Pituitary-Adrenal Axis. Trauma, Violence and Abuse 2004; 5(4): 333-352.
17. Maren S. LTP in the Amygdala: a Mechanism for Emotional Learning & Memory. Trends in Neurosciences 1999; 22: 561-567.
18. Bremner JD, Vermetten E. Neuroanatomical Changes Associated with Pharmacotherapy in Posttraumatic Stress Disorder. Ann NY Acad Sci 2004; 1032: 154-157.
19. Harmon RJ, Riggs PD. Clonidine for Posttraumatic Stress Disorder in Preschool Children. J Am Acad Child Adolesc Psychiatry 1996; 35: 1247-1249.
20. Boscarino, JA. Posttraumatic Stress Disorder and Physical Illness: Results from Clinical and Epidemiological Studies. Ann NY Acad Sci 2004; 1032: 141-153.
21. Tucker P, Ruwe WD, Masters B, Parker DE, Hossain A, Trautman RP, Wyatt DB. Neuroimmune and Cortisol Changes in Selective Serotonin Reuptake Inhibitor and Placebo Treatment of Chronic Posttraumatic Stress Disorder. Biol Psychiatry 2004; 56: 121-128.
22. Rinne T, de Kloet ER, Wouters L, Geokoop JG, de Rijk RH, van den Brink W. Fluvoxamine Reduces Responsiveness of HPA Axis in Adult Female BPD Patients with a History of Sustained Childhood Abuse. Neuropsychopharmacology 2003; 28: 126-132.
23. Davidson JRT. Pharmacotherapy of Posttraumatic Stress Disorder: Treatment Options, Long-Term follow-Up, and Predictors of Outcome. J Clin Psychiatry 2002; 61(5): 52-56.
24. Solomon SD, Gerrity ET, Muff AM. Efficacy of Treatments for Posttraumatic Stress Disorder. JAMA 1992; 268: 633-638.
25. Rivier C, Rivier J, Vale W. Stress Induced Inhibition of Reproductive Functions: Role of Endogenous Corticotrophin Releasing Factor. Science 1986; 231: 607-609.
26. Berga SL, Daniels TL, Gules DE. Women with Functional Hypothalamic Amenorrhea but not Other Forms of Anovulation Display Amplified Cortisol Concentrations. Fertil Steril 1997; 67: 1024-1030.
27. Volunteer Training Manual. Sexual Assault Centre of Edmonton. Edmonton, AB; 1999.
28. Koss MP, Figuerdo AJ. Change in Cognitive Mediators of Rape's Impact on Psychosocial Health Across 2 Years of Recovery. Journal of Consulting and Clinical Psychology 2004; 72(6): 1063-1072.
29. Brewin CR, Dalgleish T, Joseph S. A Dual Representation Theory of Posttraumatic Stress Disorder. Psychological Review 1996; 103: 670-686.
30. Frazier PA. Perceived Control and Distress Following Sexual Assault: A Longitudinal Test of a New Model. Journal of

Personality and Social Psychology 2003; 84(6): 1257-1269.
31. Girelli SA, Resick PA, Marhoefer-Dvorak S, Hutter CK. Subjective Distress and Violence During Rape: Their Effects on Long-Term Fear. Violence and Victims 1986; 1: 35-45.
32. Resnick H, Acierno R, Holmes M, Kilpatrick DG, Jager N. Prevention of Post-Rape Psychopathology: Preliminary Findings of a Controlled Acute Rape Treatment Study. Journal of Anxiety Disorders 1999; 13(4): 359-370.
33. Capital Health. Sexual Assault Response Team. Community Sector Pamphlet, March 2004; 2004.
34. Shapiro F. EMDR as an Integrative Psychotherapy Approach: Experts of Diverse Orientations Explore the Paradigm Prism. Washington, DC: American Psychological Association Books; 2002.
35. Foe EB, Steketee G, and Rothbaum B. Behavioural/Cognitive Conceptualizations of Posttraumatic Stress Disorder. Behaviour Therapy 1989; 20:155-176.
36. Rothbaum BO. A Controlled Study of Eye Movement Desensitization and Reprocessing in the Treatment of Posttraumatic Stress Disordered Sexual Assault Victims. Bulletin of the Menninger Clinic 1997; 61(3): 317-334.
37. British Crime Survey. Rape and Sexual Assault of Women: Findings from the British Crime Survey. Home Office Research Study 159:1-6 Retreived April 3 2005 from http://www.homeoffice.gov.uk/rds/pdfs2/r159.pdf; 2002.
38. Cuijpers P, Van Straten A, Smit, F. Preventing the Incidence of New Cases of Mental Disorders: a Meta-Analytic Review. J Nerv Ment Dis 2005; 193: 119-125.
39. Zoellner LA, Feeny NC, Cochran B, Pruitt L. Treatment Choice for PTSD. Behaviour Research and Therapy 41:879-886; 2003.
40. Burt MR. Cultural Myths and Supports for Rape. Journal of Personality and Social Psychology 1980; 38: 217-230.
41. Breitenbecher KH, Scarce M. An Evaluation of the Effectiveness of a Sexual Assault Education Program Focusing on Psychological Barriers to Resistance. Journal of Interpersonal Violence 2001; 16(5): 387-407.
42. Campbell R, Barnes HE, Ahrens CE, Wasco SM, Zaragoza-Diesfeld Y, and Sefl T. Community Services for Rape Survivors Enhancing Psychological Well-Being or Increasing Trauma? Journal of Consulting and Clinical Psychology 1999; 67(6): 847-858.
43. Campbell R, Wasco SM, Ahrens CE, Sefl T, Barnes HE. Preventing the "Second Rape": Rape Survivors' Experiences with Community Services Providers. Journal of interpersonal violence 2001; 16(12): 1239-1259.

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ORIGINAL ARTICLE

Knowledge, attitudes, and practices in reproductive and sexual health

Valle de los Chillos, Rumiñahui County, Province of Pichincha, Ecuador

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ABSTRACT: To help support and direct the Lions Club's construction of a Community Health Clinic specializing in Reproductive and Sexual Health, this descriptive study began in November of 2004 and was completed in May 2005. The sample consists of 552 high school students in Rumiñahui County, and surveys were used to study four principle themes: reproductive and sexual health education, family planning, sexually transmitted infections, and domestic violence. The results show a widespread lack of accurate and adequate information about reproductive and sexual health. Statistically significant variables studied include sex, age, monthly income, and age of first sexual experience. Female sex, younger age, lower monthly income, and younger age of first sexual experience all contribute to a lower quality of reproductive and sexual health, in terms of having less information about and access to these four aspects of reproductive and sexual health.

KEYWORDS: Reproductive and sexual health; Valle de los Chillos; Ecuador; sexual education; family planning; sexually transmitted infections; domestic violence

INTRODUCTION

Ecuadorians, in general, lack access to adequate information about and care for reproductive and sexual health (RSH) issues. Many authors (1,2) and organizations, including the World Health Organization and United Nations Population Fund confirm this fact (3). For instance, the infant mortality rate for the year 2000 was 45.6 per 1,000 live births (3); the percentage of births attended by health professionals, in the year 2001, was 72.6% (4); and the maternal mortality rate in 2001 dropped to 97 deaths per 100,000 live births (4).

In comparison, most developed countries have both infant and maternal mortality rates under 10 deaths per 1,000 and 100,000 births, respectively. Among adolescents, 66% of male students possess basic knowledge about RSH, while only 40% of female students do (1); 57% of 10-17 year olds have misinformation about the transmission of HIV and 31% do not know how to prevent it (2); and 33% of adolescent boys and 57% of adolescent girls who have engaged in premarital sex were forced to have their first sexual relationship (1).

In order to improve this situation in a satellite community of Quito, the Lions Club of the Valle de los Chillos acquired funding to build a Community Health Clinic specializing in reproductive and sexual health (RSH). This study defines the RSH situation in this area, focusing on: reproductive and sexual health education, family planning, sexually transmitted

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infections, and domestic violence.

METHODS

Universe and sample populations

The universe consists of high school students in fifth and sixth years (equivalent to juniors and seniors in American high schools) at the 15 high schools functioning in Rumiñahui County in the year 2002 (5). Of the 15 high schools in the county, the following seven were randomly chosen to be included in the sample: Giovanni Antonio Farina, Centro Educativo Integral, *Colegio Nacional Mixto San Rafael*, Unidad Educativa Católica Santa Ana, Unidad Educativa Darío Figueroa, *Colegio Nacional Juan de Salinas*, and *Colegio Nacional Técnico Jacinto Jijón y Caamaño*. Their participation depended on permission from the school administrators and teachers. The sample includes three public schools (italicized) and four private, but does not include any night schools. The public schools are considered "large" for the sake of this study, with over 80 students per grade level. All private schools were considered "small", with class sizes ranging from 20 to 80 students.

Five hundred and fifty-two surveys were completed by fifth and sixth year students, with a maximum of 100 surveys in large schools. In the small schools, all fifth and sixth year students who were present on the day of the study were surveyed. The number of students surveyed ranged from 21 at Santa Ana to 100 at Juan de Salinas and Jacinto Jijón y Caamaño.

Methods and data collection

The data collection consisted of a 34-question survey that lasted approximately 15 minutes. The survey focused on the four themes described earlier in this paper and determined which topics students were further interested in. All answers were exclusive (choose one and only one), with very few students choosing more than one answer. Students were surveyed during classes, with the permission of the teachers and school administrators.

To ensure the reliability of the data collection methods, all surveys were performed by the author in similar conditions. The survey was designed in Spanish by the author, with input from José Terán, pediatrician and Professor of Medicine at the Universidad Católica del Ecuador. For the purpose of receiving further input, the author translated the survey to English and received feedback from Steve Hirsch, Clinical Professor in the Department of Education Leadership and Counseling Psychology; and Anne Hirsch, Associate Dean for Academic Affairs of the Nursing School, both at Washington State University.

Execution

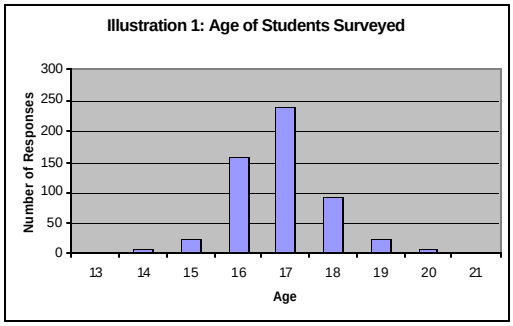
The pilot study, conducted in November of 2004, tested the effectiveness of the instruments and helped identify necessary changes. Finalized surveys were completed in March, April, and May of 2005. The principle difficulty encountered by the author during data collection was the inability to take a completely random sample of the population, due to the necessity of obtaining authorization from high school administrators and teachers. Only administrators sympathetic to the idea of this study permitted the surveys and interviews to be done. Furthermore, given that students were surveyed while in class, and that some classes were taking tests or were out of the classroom, not all eligible students were surveyed.

The biostatistics program EPI-INFO, from the Centers for Disease Control, was utilized in the processing and analysis of data. The statistical tests used to determine significance were Chi squared with the Yates correction or the Fischer exact test, when necessary. All subjects were free to refuse to participate in the study, though no student declined to complete a survey. Each phase of the study was completed with the utmost confidentiality; participants were never asked to provide identifying information.

RESULTS

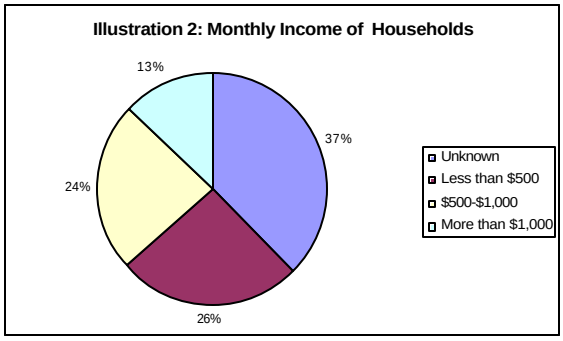
Demographic information

Of the 552 students surveyed, 237 (42.9%) are female and 315 (57.1%) are male. Their average age is 16.86 years, the median and mode is 17 years. See Illustration 1 for details:



As a measure of income, cutoff points of $500 and $1,000 (USD) were based on Ecuador's average income of $250 per person in urban areas, for the year 2002 (6). A household of two earners at the average income would yield a household income of $500, this study's maximum cutoff for "low" income. More than double this amount ($1,000) was considered "high" income. Over a third of the students did not know the monthly income of their families. Of those who did, most were considered low income, followed by middle and then

high income families (see Illustration 2).



The majority of these families have four or five people living in the household, with the number of inhabitants ranging from 2 to 13 and averaging 5.04. At the extremes, 9.1% of the students live in a house with three or fewer people and 27.6% live in a household with six or more.

The vast majority (98.2%) of the students are single, while the other 1.8% live in "free union", defined as living together but unmarried. Two hundred five (37.1%) students were in an intimate relationship at the time of the study: 38% of female students and 36.5% of male students. Thirteen students (2.4%), eight male and five female, have children.

Education/information about reproductive and sexual health

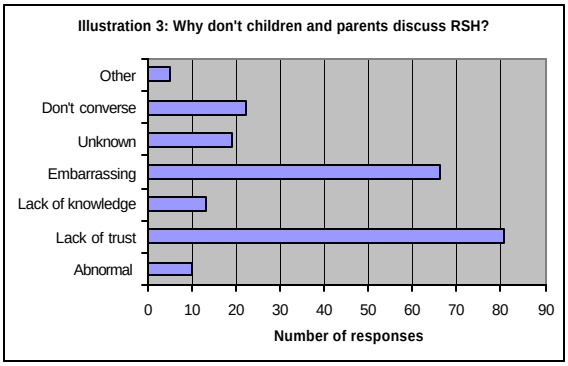
The majority of students (60.51%) believe that parents and high schools share the responsibility for their education in reproductive and sexual health matters. The complete answers can be seen in Table 1.

Table 1. Who should be responsible for educating children?

	Number of Responses	Percentage
Friends	2	0.36%
High School	3	0.54%
No one	2	0.36%
Unknown	1	0.18%
Parents	65	11.78%
Parents and High School	334	60.51%
Health Professionals	79	14.31%
Everyone	66	11.96%
Total	552	100.00%

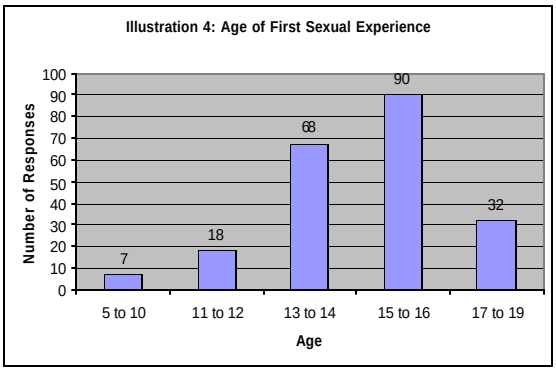
Despite the fact that 334 students believe that parents and high schools should be responsible for RSH education, only 274 actually receive RSH information from these sources (see Table 2), a difference of 10.9%. Similarly, 14.3% of students believe that health professionals should be responsible for educating them, while only 5.1% of students actually receive information from this source. In contrast, a greater proportion of students receive RSH information from friends and the media than those who believe this source should be responsible for RSH education. Table 2 describes where students receive general information about RSH, as well as information specifically about family planning. Note that only 268 students (48.6%) responded that they have received information about family planning.

Family is a crucial factor in students' level of knowledge about RSH; 336 students, or 60.9%, responded that they converse with their parents about RSH. Monthly income is a statistically significant factor ($P<0.05$) for determining whether or not families talk about RSH; families with high levels of income are more likely to converse with their children about RSH than families with low levels of income. Illustration 3 details the reasons why 39.1% of students and families do not talk about RSH.



Family planning

The majority of the students surveyed (59.3%) have not had their first sexual experience, as defined by each student. Of those who have (40.7%), the average age of their first experience is 14.58 years, see Illustration 4 for details.

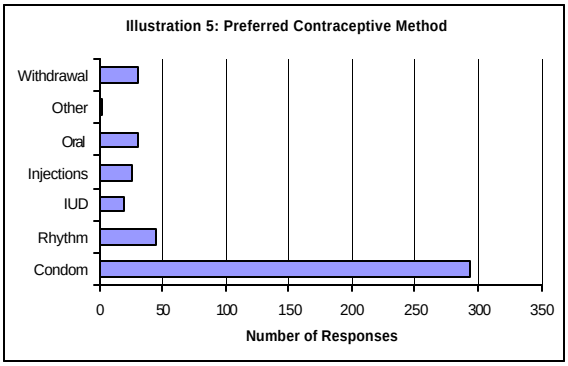


Gender is a statistically significant factor (P<0.05) for predicting the age of first sexual experience; female students are more likely than male students to wait to have their first sexual experience.

When asked their "ideal number of children", the average response was 2.06 children, with a minimum of zero, a maximum of 15, a median and mode of two. Slightly over half of the students wanted two children, while nearly a quarter wanted three.

Five hundred thirty-five students (96.9%) responded that they knew of some method of birth control. A slightly lower number, 448 students (81.5%) responded that they use, had used, or would use some method of contraceptives. Gender is a statistically significant factor in the decision to use birth control. Female students were less likely to use contraceptives than male students (P<0.05), citing reasons such as fear of side effects and the desire to have children. Nearly half of those who responded that they would not use birth control justified that response with a fear of side effects. Forty percent of respondents did not know why they would not use contraceptives and slightly over 10% said they would not use birth control because they wanted to have children.

Of students who have used, do use, or would use birth control, the condom is the preferred method, followed by the rhythm method, withdrawal, and oral contraceptives. Illustration 5 details the results.



Sexually transmitted infections

Only 62 students (11.2%) had undergone a physical exam to diagnose sexually transmitted infections (STIs), with gender and age of first sexual experience being statistically significant factors for having undergone an exam. Male students and sexually active students were more likely than female students or non-sexually active students to have had a physical exam to diagnose STIs (P<0.05 in both cases). Only 17.8% of sexually active students had undergone this type of physical exam.

Nearly all students (97.8%) had heard of some STI. Age is a statistically significant factor (P<0.05, using the Fisher exact test) for predicting if students had heard of any STI. Students older than 17 years of age were more likely to have heard of a STI, compared to students younger than 17. Though most students had heard of a STI, many did not know how to prevent them or how they are passed from one person to another. Table 3 details responses to the question, "How can you contract a STI without having sex?"

Nearly 10% of students responded that oral contraceptives provide protection from STIs and HIV/AIDS. Nearly one quarter (24.8%) believe that HIV/AIDS can be passed through everyday contact with the saliva or sweat of an infected person.

Table 2. Where do you receive information about RSH?

	General RSH Information	Percentage of Total	Family Planning Information	Percentage of Total
Friends	13	2.36%	4	1.49%
High School	78	14.13%	62	23.13%
Church	4	0.72%	9	3.36%
Media	83	15.04%	33	12.31%
None	7	1.27%	N/A	N/A
Other	3	0.54%	2	0.75%
Parents	62	11.23%	47	17.54%
Parents and High School	274	49.64%	77	28.73%
Health Professionals	28	5.07%	34	12.69%
Total	552	100.00%	268	100.00%

Table 3. How can you contract STIs without having sex?

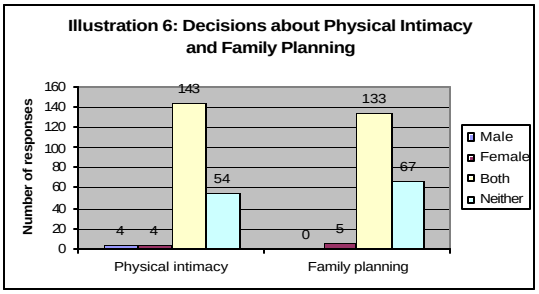
	Number of Responses	Percentage
Kisses/Handshakes	25	4.53%
Intimate Physical Contact	90	16.30%
Contact with Infected Objects	52	9.42%
Syringes/Injections	250	45.29%
Unknown	14	2.54%
Other	3	0.54%
Blood	118	21.38%
Total	552	100.00%

Exactly half of the students responded that they knew how to correctly use a condom, and nearly half (49.8%) responded that they would be embarrassed to buy a condom, while 23.4% would be embarrassed to use one. Gender and sexual experience are statistically significant factors ($P<0.05$) for feeling embarrassed to buy a condom. Female students and those who had not yet had their first sexual experience were more likely to be embarrassed to buy and/or use a condom than male students or those who had had their first sexual experience.

Domestic violence

During the month prior to the study, physical or verbal aggression occurred in 20.8% of students' homes. Adolescents who have witnessed domestic violence are more likely to be involved in a violent relationship in the future, as are those involved in a relationship with an unequal distribution of power. Two questions asked students in an intimate relationship who was responsible for making decisions about physical intimacy and family planning. The majority responded that neither partner makes these decisions.

Another interesting component of this power dynamic in a relationship is the likelihood of young people to say no to a partner requesting sex. In this study, 23.4% of students believe that it is not okay to refuse to sex under any circumstance, 27.6% believe that it is okay at any time, and the other 49.0% believe that it depends on the situation.



DISCUSSION

The results of this study confirm data found in other studies, primarily that "sexuality and fertility are some of the severest taboos" (3) and that "adolescents lack sources of reproductive and sexual health education. Also, mothers and fathers do not respond to their adolescents' questions about sexuality because of embarrassment and a lack of knowledge" (3). The findings that most specifically support these statements are that:

- under half of students responded that they had received information about family planning,
- approximately 40% of students do not converse with their parents about RSH,
- half of students said they would be embarrassed to purchase a condom, and
- approximately two-thirds of students in a relationship respond that neither they, nor their partners, make decisions regarding physical intimacy or family planning.

This last point is particularly important because open conversation, along with accurate information, is critical to enjoying healthy and safe relationships.

Female students, more than male students, seem to bear the burden of this lack of information and access to quality RSH. For instance, the fact that the majority of students with children are male is because pregnant students lack the support from administrators and teachers necessary to stay in school. Strong social taboos also dictate that pregnant adolescents drop out of school in order to raise the child. Further, females tend to be the victims of both sexual abuse and domestic violence. Though sexual abuse was not directly studied, the young ages at which some students had their first sexual experience (ages 5 to 12, for instance) suggest that these relationships may not have been consensual. The levels of domestic violence cited by the students are most likely underestimates of reality, as aggression or violence may have occurred without the student's realization, or in the month before the study.

It is difficult to compare this study's findings to similar quantitative data because very few studies have focused on the RSH of adolescents in Ecuador. In comparison with the studies of Francisco Sevilla and Nelson Oviedo Valdivieso, the students in this study tend to have a higher level of knowledge about RSH issues, particularly family planning and STIs. Perhaps this can be explained with a difference of one to two years between the studies, but it seems more probable that results differed because of a difference in sample diversity. These authors studied the entire country, while this study focused on the relatively small

geographic area of Valle de los Chillos.

The author would like to note that in the original study, a number of students, as well as high school teachers from these schools and market vendors from the same area participated in in-depth interviews about the same four RSH variables addressed in the surveys. The results of these interviews are not included in this paper, due to sampling concerns and space constraints, but did add richness and understanding to the study that cannot be conveyed through strictly quantitative methods. Though addressing these topics through qualitative methods is difficult due to the intensity of the social taboos surrounding RSH, future research could involve focus groups, interviews, or ethnographies, in order to paint a more nuanced picture of the RSH challenges facing this population.

CONCLUSION

This study makes it clear that adolescents in the Valle de los Chillos, Ecuador, suffer from a poor quality of reproductive and sexual health, measured in terms of RSH education and information about RSH, family planning, sexually transmitted infections, and domestic violence. Despite the efforts of many organizations and individuals, misunderstandings about RSH persist and, coupled with inadequate support systems for these students, negatively impact their quality of life. The solution with the greatest potential to impact the concern of poor RSH is also the most complicated: to minimize the social taboos surrounding RSH and open avenues of communication to enable students to obtain necessary information.

Education programs that address RSH should not only involve adolescents, but also must be directed towards the parents and teachers, who often lack accurate information. Parents and teachers should also be taught various ways to approach the topic and stimulate fruitful discussion. Because we have seen that females often bear the greatest burden due to a lack of understanding about RSH, programs designed to address the RSH in this population must be aware of and prepared to address this disparity. For instance, supportive and educational services should be provided to pregnant adolescents, their families, and their schools, in order to enable these women to continue their education. Further, a community center must also provide educational and psychological services for teen victims of sexual abuse and/or domestic violence.

Though this study found a number of areas in which the students lack accurate information, and any presentation of basic information about family planning methods, sexually transmitted infections, and domestic violence would be an improvement on the current level of knowledge, the following three recommendations address the most pressing areas of concern:

1. Present information about family planning methods that do not have significant side effects. For those methods that do cause side effects, provide statistics about the number of users that experience these side effects, as well as the severity of these reactions.
2. Clarify how sexually transmitted infections can be prevented and how they are passed between people. Describe symptoms of common STIs and emphasize that all sexually active students should receive exams to check for STIs, regardless of the presence of symptoms.
3. Promote self respect and respect between partners to enable more open discussion about RSH issues within the context of an intimate relationship. Stress the importance of discussing issues related to physical intimacy and family planning.

Addressing these topics through consistent, open communication between students, teachers, and families will be the most effective method of addressing the poor quality of RSH in this population.

ACKNOWLEDGEMENTS

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REFERENCES

1. Sevilla, Francisco. March. Aportes al marco teórico de la educación y salud sexual y reproductiva. Correo Poblacional: Salud Reproductiva y Gerencia en Salud 2003; 11(1): 16-18.
2. Oviedo Valdivieso, Nelson y Ordóñez Sotomayor, José. Situación de los Adolescentes y jóvenes en el Ecuador. Quito: Centro de Estudios de Población y Desarrollo Social 2003: 17.
3. World Health Organization. WHO Home Page. www.who.org Accessed Feb2004.
4. Instituto Ecuatoriano de Seguridad Social (IESS). IESS Home Page. www.iess.gov.ec. Accessed Feb 2004.
5. Gobierno del Cantón Rumiñahui. Plan estratégico participativo del cantón Rumiñahui: 2002-2022. Quito: Consejo Municipal del Cantón Rumiñahui 2002; May: 59, 93.
6. Instituto Nacional de Estadística y Censo (INEC), Ecuador. INEC Home Page. www.inec.gov.ec. Accessed Feb 2004.
7. United Nations Population Fund. Country Overview: Ecuador. http://www.unfpa.org/profile/ecuador.cfm. Accessed May 2005.
8. Ambrossi, Rodrigo Tenorio. La Intimidad Desnuda: Sexualidad, Cultura Indígena y Salud Reproductiva. Quito: Pan-American Health Organization/World Health Organization 1996 March.
9. Ashford, Laurie. New Population Policies: Advancing Women's Health & Rights. Population Bulletin, Population Reference

Bureau 2001 March; 56: 3-42.
10. Bacarreza Schulze, Johnny Carlos. Espacios de debate y diálogo con y para población adolescente en el marco del Programa de Salud Sexual y Reproductiva [Thesis]. Quito: Pontificia Universidad Católica del Ecuador, School of Medicine; 2002.
11. Barros, Teodoro; Barreto, Dimitri; Pérez, Freddy; Santander, Rocío; Yépez, Eduardo; Abad-Franch, Fernando et al. Un modelo de prevención primaria de las enfermedades de transmisión sexual y del VIH/SIDA en adolescentes. Revista Panamericana de la Salud Pública 2001; 10(2).
12. Bertrand, Jane T; Bull, Sheana E.; Glavez, Roberto Santiso; Rosen, James E.; Terbough, Anne Terceros. Family Planning Among Indigenous Populations in Latin America. International Family Planning Perspectives 1995 Dec; 21: 145+.
13. Blum, Agustín Cuesta. El involucramiento del varón bajo una perspectiva de género en los servicios de APROFE. Correo Poblacional: Salud Reproductiva y Gerencia en Salud 2003 March; 11(1).
14. Camacho Soria, María Marisol. Salud reproductiva en mujeres adolescentes jefes de hogar: investigación realizada en Fundación Tierra Nueva [Thesis]. Quito: Pontificia Universidad Católica del Ecuador, School of Social Work; 2001.
15. Center for Reproductive Law and Policy (CRLP). Women of the World - Laws and Policies Affecting their Reproductive Lives - Latin America and the Caribbean. CRLP 1997: 38-42.
16. CIA World Factbook. Ecuador Page. http://www.cia.gov/cia/publications/factbook/. Accessed April 2004.
17. Country Report on Human Rights Practices - 2000: Ecuador. United States Government, 2001 Feb.
18. Donaldson, Loraine. Fertility Transition: The Social Dynamics of Population Change. Cornwall, England: TJ Press; 1991.
19. Escobar Koziel, Luis Fernando. Investigación Científica para Médicos. Quito: Pontificia Universidad Católica del Ecuador, School of Medicine; 1999 Sept.
20. Family Health International. Women's Voices, Women's Lives - The Impact of Family Planning. Family Health International; 1998.
21. Goicolea, Isabel. Exploring women's needs in an Amazon region of Ecuador. Reproductive Health Matters 2001 May; 9: 193+.
22. Hilfinger Messias, Deanne; Im, Eun-Ok; Page, Aroha; Regev, Hanna; Spiers, Judith; Yoder, Laurie; et al. Defining and Redefining Work: Implications for Women's Health. Gender and Society 1997 June; 11: 296-323.
23. Hungría, Miriam Becerra. Mujer y VIH/SIDA. Correo Poblacional: Salud Reproductiva y Gerencia en Salud 2003 June; 11(2).
24. International Planned Parenthood Federation. IPPF Home Page. www.ippf.org. Accessed April 2004.
25. Macintyre, Kate; Bilsborrow, Richard E.; Olmedo, Caton; y Carrasco, Rodolfo. Rapid surveys for program evaluation: design and implementation of an experiment in Ecuador. Revista Panamericana de la Salud Pública 1999; 6 (3).
26. Matthews, Stephen; Ribar, David; Wilhelm, Mark. The Effects of Economic Conditions and Access to Reproductive Health Services on State Abortion Rates and Birthrates. Family Planning Perspectives1997 March-April; 29: 52-60.
27. Morgan, Lynn M. Imagining the Unborn in the Ecuadorian Andes. Feminist Studies 1997 Summer; 23: 335+.
28. Muñoz Izquierdo, Carlos and Núñez Gornés, María de los Ángeles. Desarrollo de una Propuesta para la Construcción de Indicadores del Impacto Social de la Educación en América Latina y el Caribe. México, DF: Universidad Iberoamericano Press.http://www.prie.cl/espannol/seccion/documento/ind_impact_soc.pdf. Accessed Jan 2003.
29. Oviedo Valdivieso, Nelson. Salud y derechos sexuales y reproductivos y reforma del sector salud. Correo Poblacional: Salud Reproductiva y Gerencia en Salud 2003 Sept; 11.
30. Pan-American Health Organization. PHO Home Page. www.paho.org. Accessed Feb 2004.
31. Pan-American Health Organization. Perfil de Salud de País: Ecuador, 1998-2001. http://www.paho.org/Spanish/SHA/prflECU.htm. Accessed Nov. 2004.
32. Pan-American Health Organization. Violencia, un problema de salud pública que ya es pandemia. http://www.opsecu.org/bevestre/revistas/violencia.pdf. Accessed 2004 Nov.
33. Remez, L. Both Contraceptive Use and Unplanned Births Are Common in Ecuador. International Family Planning Perspectives 1996 June; 22: 85-6.
34. Trakas, D.J. y Sanz E., eds. Childhood and medicine use in a cross-cultural perspective: A European concerted action. Luxembourg: European Commission, Directorate-General Science, Research and Development; 1996.
35. United Nations. Human Development Report 2003 website. www.un.org. Accessed Jan 25 2004.
36. United Nations Economic and Social Council. La Mujer en el año 2000: igualdad entre los géneros, desarrollo y paz para el siglo XXI: consecución de los objetivos estratégicos, adopción de medidas en las esferas de especial preocupación y medidas e iniciativas ulteriores: el papel de los hombres y los niños en el logro de la igualdad entre los géneros" 2004 March: 1-12.
37. United Nations Population Fund. Estado de la población mundial 2003. www.unfpa.org/upload/lib_pub_file/223_filename_swp2003_spa.pdf. Accessed Nov. 2004.
38. United Nations Population Fund. Proyectos y programas propuestos; Recomendación de la Directora Ejecutiva; Asistencia al Gobierno del Ecuador. New York: UNFPA; 2001 Jan 29-Feb 6.
39. United Nations Population Fund. The State of World Population 1997. www.unfpa.org/swp/1997/chapter1.htm. Accessed Nov 2004.
40. World Bank. World Bank Home Page. www.wb.org. Accessed Feb2004.

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ORIGINAL ARTICLE

Morbidity profile and prescribing patterns among outpatients in a teaching hospital in Western Nepal

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ABSTRACT: Background: Recent studies on prescribing among outpatients in hospitals in Western Nepal are lacking. The main objectives of the study were to obtain information on the morbidity pattern among outpatients and to analyze prescribing using drug use indicators. Methods: A retrospective hospital record based study from 01.01.2004 to 31.12.2004 was carried out among individuals attending the outpatient department (OPD) of the Manipal Teaching hospital, Pokhara, Western Nepal. A total of 32,017 new patients attended the OPD during the study period. Systematic random sampling (1 in every 20 patients) was done and 1600 patients selected. After excluding patients visiting the emergency department, those who got admitted and whose records were not available, 1261 cases were analyzed. The demographic details, morbidity pattern, average number of drugs prescribed, percentage of drugs prescribed by generic names and from the Essential drug list of Nepal (Essential drugs are those which satisfy the priority healthcare needs of the population), percentage of encounters with an antibiotic and an injection prescribed were noted.

Results: 1261 patients made 1772 visits. Upper respiratory tract infection and acid peptic disease were the most common diagnoses. The mean number of drugs was 1.99. Only 19.5% and 39.6% of drugs were prescribed by generic name and from the Essential drug list. Antibiotics and injections were prescribed in 26.4% and 0.96% of encounters. Cetrizine, vitamins, amoxicillin, the combination of paracetamol and ibuprofen and ranitidine were most commonly prescribed.

Conclusions: Upper respiratory tract infections and acid peptic disease were the common illnesses. Generic prescribing and use of essential drugs were low. Some of the drug combinations being used were irrational. Prescriber education may be helpful in encouraging rational prescribing.

KEYWORDS: Drug use review, drug utilization, morbidity patterns, outpatients

INTRODUCTION

Drug utilization research has been defined by the World Health Organization (WHO) as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (1). The assessment of drug utilization is important for clinical, educational and economic purposes (2). Prescribing patterns need to be evaluated periodically to increase the therapeutic efficacy, decrease adverse effects and provide feedback

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to prescribers (3,4). Drug utilization reviews are useful for obtaining information about drug use patterns and for identifying high cost drugs (5).

Irrational and inappropriate use of drugs is a major concern in both developed and developing countries (6,7). The cost of irrational use of medicines is enormous in terms of scarce resources and the adverse clinical consequences of therapies that may have real risks but no objective benefits.

Previous studies in our hospital had shown deficiencies in use of medicines (8,9). The problems observed were that most of the drugs were prescribed by brand names and the number of drugs prescribed from the Essential drug list was low. The World Health Organization (WHO) defines essential drugs as those that satisfy the health care needs of the majority of the population. They should therefore be available at all times in adequate amounts and in the appropriate dosage forms. Lately, the term 'drugs' has been replaced by 'medicines'. A number of interventions have been recently introduced at the Manipal Teaching hospital (MTH) to ensure more rational use of medicines (10). The terms 'inappropriate' and 'irrational' are often used interchangeably. The drugs chosen may not be appropriate to the patient, the diagnosis, economic status etc. The conference of experts on the rational use of drugs, convened by the WHO in Nairobi in 1985 defined that "Rational use of drugs requires that patient receive medication appropriate to their clinical needs, in doses that meet their own individual requirement for an adequate period of time and at the lowest cost to them and their community."

A previous study was carried out to obtain information on the prescribing patterns among medical outpatients (9). However, information on the morbidity pattern and prescribing patterns of drugs among out patients in other specialties are lacking in Western Nepal. A previous study was carried out around five years back with a rather limited time window, hence the usefulness of the present study. The objectives of the study were to evaluate prescribing patterns using drug use indicators and obtain information on the demographic characteristics and morbidity patterns of patients attending the outpatient department (OPD) during the study period. Information on the demographic characteristics and the morbidity patterns will help in determining what diseases were common in different age groups and genders. Proper prescribing habits and rational use of medicines can play a significant role in ensuring quality care in MTH and other healthcare facilities.

METHODS

The study was carried out at the Manipal Teaching hospital, a tertiary care hospital attached to the Manipal College of Medical Sciences, Pokhara, Nepal. The retrospective hospital record based study was carried out over a one year period of January 1st 2004 to December 31st 2004.

New patients attending the outpatient department (OPD) of MTH during the study period were considered for analysis. Follow up visits during the study period were included and were counted as separate visits. Visits for a new diagnosis by the selected patients during the study period were not considered. A total number of 32,017 patients attended the OPDs during the study period. Of this, 5% (1600 cases) (1 in every 20) were selected by systematic random sampling. In systematic random sampling, first a number within the sampling interval (twenty in our study) is chosen using random number tables. We chose a random number between 1 and 20. Then every 20th patient following the first number chosen was selected from the outpatient register maintained in the medical records department (MRD).

Patient visiting the emergency department or who got admitted during the OPD visit were not included in the study. We expected that their prescribing patterns may be substantially different from those of ambulatory patients. Records not available in the medical records department were excluded from the study. After all these exclusions, a total of 1261 cases were analyzed.

The age, sex, address and occupation of the patients were noted. The diagnosis/diagnoses were noted and the prescribing patterns of the drugs were analyzed. The patients were grouped into the age groups of <1 year, 1-5 years, 5-15 years, 15-25 years, 25-35 years, 35-45 years, 45-55 years, 55-65 years and above 65 years. We selected this particular age distribution as we wanted to study the infants and under-five populations as a separate age group. Under-five morbidity and mortality is a major health problem in Nepal. The percentage of individuals in each age group was calculated. The commonly occurring classes of diseases according to the International Classification of Diseases (ICD 10) were noted. Most common diseases were found out for each age group.

The average number of drugs per encounter was calculated. The percentage of drugs prescribed from the Essential drug list of Nepal was calculated. The percentage of drugs prescribed by generic name was noted (11). The percentage of fixed-dose combinations (FDCs) prescribed was noted. The components of the FDCs were detailed. The ten most commonly prescribed group of drugs and individual drugs were detailed. The ten most commonly prescribed antibiotics were recorded. The percentage of encounters with an antibiotic and an injection prescribed were calculated.

Among the antibiotics, the frequency of prescribing of different groups of antibiotics was studied. Among the FDCs the preparations containing at least one antibiotic, one non-steroidal anti-inflammatory drug (NSAID) or one corticosteroid or combinations of these were noted. These are common components of FDCs and many preparations contain these drugs either individually or in combination.

The relevant authorities were kept informed. However, ethical clearance was not obtained for the study. The data analysis was carried out manually. The data was expressed as percentage, mean and total numbers.

RESULTS

A total of 1261 files were analyzed. The catchment area of our hospital is Pokhara city, Kaski district in which Pokhara is situated and the neighboring districts of Syangja, Tanahu, Parbat and Baglung. The hospital also gets patients from the mountain districts of Mustang and Manang and the hill district of Gorkha.

Six hundred and eighty patients (53.9%) were female. The age group 15-25 years accounted for the highest number [364 (28.9%)] of patients. The age distribution of outpatients is shown in Figure 1. Only 909 patient files (72.1%) contained information on the occupation of the patients. Students were the largest group to visit the OPD [398patients (43.8% of the 909 patients)]. The distribution of patients by occupation has been shown in Table 1.

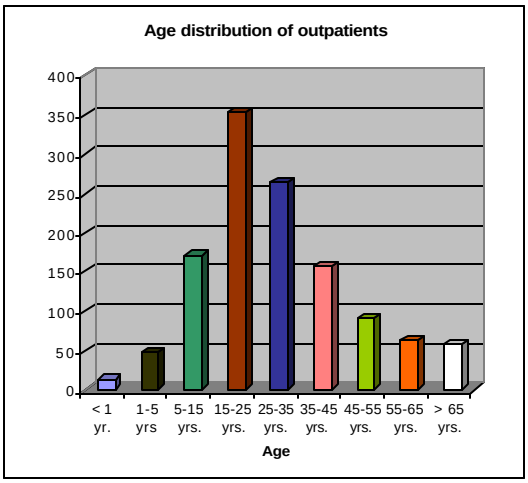

Figure 1. Age distribution of outpatients

The 1261 patients had made 1772 visits during the study period. Diseases of the skin and soft tissues [237 patients (18.8%)] (which included tinea infection, acne vulgaris, scabies, and musculoskeletal pain) were the most common. Other groups of diseases in decreasing frequency were diseases of the digestive system (175 patients), diseases of the respiratory system (160 patients), and infectious and parasitic diseases (145 patients). Diseases of the genitourinary system (127 patients) were also common. Mental disorders and behavioral problems were seen in 31 patients. Many patients had more than one diagnosis. In cases of multiple diagnoses, the diagnosis/es for which treatment was given during the visit were noted. 15.96% of the files did not have any diagnosis written. The missing diagnoses were classified as 'diagnosis not written'. The common individual illnesses among outpatients are shown in Table 2. Going by the age group, tinea infection was the most common illness in the age group < 1 year, impetigo in the 1-5 year age group, upper respiratory tract infection (URTI) was the most common illness in the 5-15, 15-25, 25-35 and 35-45 year age groups. Acid peptic disease (APD) was most common in the age group of 45-55 years and COPD in the age groups 55-65 years and more than 65 years.

The total number of drugs prescribed was 3532. The oral dosage form accounted for 71.9% of drugs while 27.5% were prescribed in the topical form. The mean ± SD number of drugs per prescription was 1.99 ± 1.25. Only 19.5% drugs were prescribed by generic names. At least one antibiotic was prescribed in 468 of the 1772 encounters (26.4%). Seventeen encounters (0.96%) had at least one injection prescribed. A total of 21 injections were prescribed. The common injections prescribed were tetanus toxoid followed by triamcinolone. Only 1399 drugs (39.6%) were prescribed from the Essential drug list of Nepal.

Table 1. Distribution of patients by occupation

Occupation	Number of patients (percentage of total patients) N= 909*
Students	398 (43.8)
House wives	208 (22.9)
Farmers	148 (16.3)
Office job holders	61 (6.7)
Others	94 (10.3)

* Only 909 patient files contained information on occupation

Groups of drugs which were commonly prescribed were antihistamines [251 prescriptions (7.1% of the 3532 drugs prescribed)], NSAIDs (6.8%) and anti ulcer drugs (6.1%). The most commonly prescribed groups of drugs have been shown in Table 3. The most frequently prescribed individual drugs were cetrizine [226 prescriptions (6.4%)], multivitamin preparations (3.7%), amoxicillin (3.1%) and the FDC of paracetamol

& ibuprofen (2.7%). The ten most commonly prescribed individual drugs are shown in Table 4.

Table 2. Most common diagnoses among outpatients

Diagnosis	# of cases (% total patients) N= 1261*
Upper respiratory tract infections	153 (12.1)
Acid peptic disease	81 (6.4)
Tinea infection	57 (4.5)
Acne vulgaris	41 (3.2)
Scabies	36 (2.8)
Musculoskeletal pain	28 (2.2)
Conjunctivitis	28 (2.2)
Otitis media	28 (2.2)
Chronic obstructive pulmonary disease	26 (2.1)
Dental caries	26 (2.1)

* Diagnosis was not available in the case record of 201 patients

Table 3. Most commonly prescribed groups of drugs among hospital outpatients

Group of drugs	Number (% of total) N = 3532	
Antihistaminics	251	(7.1)
NSAIDs	248	(6.8)
Anti ulcer drugs	215	(6.1)
Antifungal agents	180	(5.1)
Corticosteroids	156	(4.4)
Antidepressants	82	(2.3)
Drugs acting on skin + mucous membrane	66	(1.9)
Nasal decongestants	65	(1.8)
Antiprotozoals	62	(1.75)
Antihelminthics	59	(1.7)

Antibiotics were a commonly prescribed group of drugs and accounted for 582 of the 3532 drugs (16.5%) prescribed. The most commonly prescribed groups of antibiotics were the penicillin group [213 of the total of 582 antibiotics (36.6%)] followed by quinolones (19.6%), macrolides (11.7%), tetracyclines (8.8%), and aminoglycosides (4.5%). The most commonly prescribed individual antibiotics were amoxicillin [111 prescriptions (3.1% of the 3532 drugs prescribed)] followed by the fixed dose combination (FDC) of ampicillin and cloxacillin (2.3%) and ciprofloxacin (2.2%). Other commonly prescribed antibiotics were doxycycline, erythromycin and norfloxacin. The most commonly prescribed antibiotics are detailed in Table 5. FDCs accounted for 559 of the 3532 drugs (15.8%) prescribed. Only 4.5% of FDCs were from the Essential drug list of Nepal. The most common FDCs were multivitamin preparations (3.7% of the 3532 drugs), paracetamol and ibuprofen (2.7%), cyproheptadine and tricholine citrate (1.5%), clotrimazole and tinidazole (1%) and a combination of chlorbutanol, polyvinyl alcohol and povidone iodine (0.85%). These combinations were prescribed by brand names.

Table 4. Most commonly used drugs among hospital outpatients

Drug	Number (% of total) N = 3532	
Cetrizine	226	(6.4)
Multivitamin preparations	131	(3.7)
Amoxiclin	111	(3.1)
Paracetamol + Ibuprofen	95	(2.7)
Ranitidine	88	(2.5)
Ampicillin + Cloxacillin	83	(2.3)
Diclofenac	79	(2.2)
Ciprofloxacin	78	(2.2)
Clotrimazole	61	(1.7)
Omeprazole	57	(1.6)

Of the combination preparations, 110 of the 559 preparations contained at least one NSAID, 36 preparations contained at least one antibiotic while 31 preparations contained at least one corticosteroid.

The prescribing indicators among outpatients are shown in Table 6.

DISCUSSION

The age distribution of the patients showed that the age group of 15-25 years constituted 28.9% of patients followed by the age group of 25-35 years and 5-15 years (Fig. 1). The distribution corresponds to that observed in the 2001 population census of Nepal (12). Young patients accounted for the majority of patients attending the OPD. The large population of young patients attending the OPD was also observed in a previous

study (9). A possible reason could be the high proportion of young people in the population and also the fact that patients attending the emergency and who were admitted were not included. A greater proportion of older patients have been seen among in-patients in previous studies.

Table 5. Most commonly prescribed antibiotics among hospital outpatients

Drug	Number (% of total) N= 3532	
Amoxicillin	111	(3.1)
Ampicillin + Cloxacillin	83	(2.3)
Ciprofloxacin	78	(2.2)
Doxycycline	48	(1.4)
Erythromycin	35	(1)
Norfloxacin	21	(0.6)
Fusidic acid	19	(0.54)
Clarithromycin	16	(0.4)
Sisomycin	13	(0.36)
Azithromycin	11	(0.3)

Table 6. Prescribing indicators among outpatients

Parameter	Value
Total number of patients analyzed	1261
Total number of visits made for new diagnoses during the period	1772
Total number of drugs prescribed	3532
Average number of drug per encounter	1.99
% of drugs prescribed by generic name	19.2
% of encounters with an antibiotic prescribed	26.4
% of encounters with an injection prescribed	0.96
% of drugs prescribed from the Essential drug list of Nepal	39.6
% of FDCs prescribed	15.8

Skin disease was the most common indication for visiting the OPD followed by diseases of the digestive and respiratory system. Infectious and parasitic diseases were common. The common individual diseases were URTI, APD, tinea infection, acne vulgaris and scabies. The common illnesses accounting for OPD visits in the Western development region, in which Pokhara city is situated, were skin diseases, acute respiratory infections (ARI), diarrheal diseases, intestinal worms, gastritis and pyrexia of unknown origin (PUO) (13). In a study from a primary health centre in Duwakot near Kathmandu, viral fever, cut/injuries, hypertension, worm infestation and APD were the more common diseases (14).

The diseases listed above, with the exception of hypertension, are diseases of poverty and may be indicative of low socioeconomic development. Infectious diseases keep people in poverty. Worm infestation and respiratory diseases are common in poor developing countries. The big three infectious diseases-HIV/AIDS, TB and malaria claimed 5.7 million lives worldwide in 2001 (15). Ongoing ill health is a major reason why the poor are not able to break out of the cycle of poverty. Infections leads to poverty, poverty leads to infections (15).

The average number of drugs per prescription was 1.99. Our number is less than the 2.2 drugs per prescription noted in the Terai districts and the 2.1 drugs noted in the hill districts of Nepal (16). At the Manipal Teaching hospital, patients have to pay for their consultation, diagnostic tests or procedures and medicines. Poor in-patients often have their ward and laboratory charges waived and are supported by the Poor Patients' fund. These support facilities are not generally available to outpatients. In a previous study among medical outpatients, the mean number of drugs was 2.15 (9). In a study in a general hospital in Nigeria, the average number of drugs per prescription was 3.16 among outpatients (17). In Uzbekistan, rural primary physicians had prescribed 2.9 drugs per patient (18). The lower number of drugs noted in our hospital is a welcome sign and has to be encouraged. There may be an increased compliance, lower cost of therapy and decreased risk of drug interactions when lesser number of drugs are prescribed. However, we did not investigate whether diseases are being treated by alternative means and, we also did not look into the rationality of prescriptions. Thus, we could not conclude that the low number of drugs was not simply secondary to misuse or under treatment.

Only 19.2% of drugs in our study were prescribed by generic name. In a previous study, 32.6% of drugs were prescribed generically (9). Sarkar et al. had previously observed that 24.4% of drugs were prescribed by generic name (8). In previous studies, in other locations the percentage prescribed by generic name ranged from 38% to 51% (18,19). The decreasing percentage of drugs prescribed by generic names in our hospital is a matter of concern and the reasons for these should be investigated. Generic prescribing decreases the risk of wrong medicines being given to patients as many

medicines with different generic names have similar brand names. Generic medicines are however, not being widely manufactured in Nepal. There is substantial price variation between brands and on prescribing by generic name, the pharmacist can dispense a cheaper brand reducing the cost of treatment.

Antibiotics and injections were prescribed in 26.4% and 0.96% of encounters respectively. Studies have shown that antibiotics and injections were prescribed in respectively 45.2% and 3.2% of encounters in the hill districts of Nepal (16). In a previous audit of prescriptions, antibiotics were prescribed in 47.8% of encounters (9). In Nigeria, antibiotics were prescribed in 50.3% of encounters (17). The lower number of encounters with an antibiotic or injection prescribed is a welcome sign and has to be encouraged (to be discussed subsequently). Also, only disposable needles are used in MTH and the risk of spread of blood borne infections has been reportedly decreased.

Only 39.6% of drugs were prescribed from the Essential drug list of Nepal. In a previous study, 62.5% of drugs were prescribed from the Essential drug list (11). In a previous study at primary healthcare facilities in the Kaski district, the percentage of drugs prescribed from the Essential drug list varied from 70.9% to 74% (20). The low rate of prescribing of essential drugs is a matter of concern. Excessive use of multivitamin and combination preparations may be one of the factors responsible. The use of the antihistamine cetrizine, which is not on the Essential drug list, may be another contributory factor. It must be noted though that Essential drugs are primarily meant for primary healthcare systems while we studied drug utilization in a tertiary care hospital.

The most commonly used antibiotics were amoxicillin, FDC of ampicillin and cloxacillin and ciprofloxacin. In a previous study, the most frequently prescribed antibiotics were ampicillin, chloramphenicol and gentamicin (21). In medical outpatients, the most commonly prescribed antibiotics were amoxicillin, metronidazole, the FDC of metronidazole and diloxanide furoate and norfloxacin (9).

The antibiotics used in our hospital were older generation antibiotics and this is to be welcomed. However, the use of the FDC of ampicillin and cloxacillin is a matter of concern.The use of antibiotics should be in accordance with the sensitivity patterns of microorganisms in the particular area (22). If the organisms are sensitive to older antibiotics they should be used. The newer antibiotics are expensive and patients may not be able to afford a full course and they may opt for a truncated course increasing the likelihood of resistance. The newer antibiotics should be kept in reserve. Also, more data is available for older antibiotics which have been used in a larger number of patients and for a longer period of time. The FDC of ampicllin and cloxacillin often does not contain the requisite amount of each individual antibiotic. The combination is not synergistic as cloxacillin is not active against gram negative bacteria and does not inhibit beta lactamase while ampicillin is not active against staphylococci. Thus, the combination only adds to the cost and adverse effects of both drugs.

Antibiotics, antihistamines, NSAIDs, anti-ulcer drugs and corticosteroids were the group of drugs most commonly prescribed. In a previous study, antimicrobials, analgesics, and cough and cold remedies were most commonly prescribed (9). In a study in Duwakot health center, antipyretics, antibiotics and NSAIDs were most commonly prescribed (14). The use of drugs was in accordance with the high prevalence of infectious, skin and parasitic diseases among outpatients in our study.

FDCs accounted for 15.8% of drugs prescribed. In a previous study, FDCs accounted for 47% of drugs (9) while in Uttaranchal, India, FDCs accounted for 59% of drugs prescribed (19). However, a problem noted was the use of irrational drug combinations in a few instances. Irrational combinations are those which contain a combination of drugs which may be used to treat a condition without arriving at a proper diagnosis. Combinations of antifungals, antibiotics and corticosteroids are available especially among dermatological preparations. The FDC may not contain the requisite amount of each individual drug and the combination may not be synergistic. Moreover, the FDCs were usually prescribed by brand name and this may be another factor responsible for the low percentage of drugs prescribed by generic names.

In Pokhara city, most medicines are available. Also the hospital pharmacy maintains adequate inventory and ensures adequate supply of medicines during the frequent bandhs (a form of political protest) and blockades. The hospital drug and therapeutics committee (DTC) has already taken note of the results of this and other studies. Generic prescribing is being strongly encouraged, the number of brands available in the pharmacy has been limited and newer drugs can be introduced in the hospital only after approval by the DTC. The information obtained from this study gives base line data on prescribing to outpatients and will be helpful to evaluate the effect of future and ongoing interventions, both managerial and educational.

Our study had many limitations. The mean cost of drugs and the mean duration of prescription were not calculated. The diagnosis was not available in a substantial number of prescriptions. The rationality of prescriptions was not looked into. The study was

retrospective and non-drug treatments for different conditions were not analyzed. The study population was young. The results may not be comparable to those obtained from other centers where the patients may be sicker and on multiple medicines. A prospective study interviewing the outpatients may be considered. These limitations may impact on the generalizability of the results obtained.

CONCLUSION

Infectious diseases and parasitic infestations were common and this may be associated with low socioeconomic development. The average number of drugs per prescription was low but prescribing by generic names has to be encouraged. The use of essential drugs was low and the FDCs used were not rational in some cases.

Framing of standard treatment guidelines for common diseases and prescriber education regarding rational use of medicines as has been done in many hospitals may be helpful.

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REFERENCES

1. World Health Organization. Introduction to drug utilization research. Oslo: 2003.
2. Uppal R, Nayak P, Sharma PL. Prescribing trends in internal medicine. Int J Clin Pharm Ther Toxicol 1984; 22:373-376.
3. Krishnaswamy K, Dinesh Kumar B, Radhaiah G. A drug use survey- precepts and practice. Eur J Clin Pharmacol 1985; 29:363-370.
4. Pradhan SC, Shewade DG, Shashindran CH, Bapna JS. Drug utilization studies. National Med J India 1988; 1:185-189.
5. Marshner JP, Thurmann P, Harder S, Rietbrock N. Drug utilization review on a surgical intensive care unit. Int J Clin Pharmacol Ther 1994; 32:447-451.
6. Hogerzeil HV. Promoting rational prescribing: an international perspective. Br J Clin Pharmacol 1995; 39:1-6.
7. Joshi MP. Rational prescribing. In: Joshi MP, Adhikari RK, eds. Manual of drugs and therapeutics. Kathmandu: Health Learning Materials Centre 1996:1-10.
8. Sarkar C, Das B. Prescribing trends in a teaching hospital in Western Nepal. Journal of Nepalgunj Medical College 2:4-5; 2002.
9. Shankar PR, Partha P, Nagesh S. Prescribing patterns in medical outpatients. Int J Clin Pract 2002; 56:549-551.
10. Mishra P. Enhancement of consumer safety and rational use of drug: an important role of Drug and Therapeutics Committee (DTC). HAI News 2005; 132:21-22.
11. Department of Drug Administration. National list of essential drugs, Nepal (Third revision). Kathmandu: 2002.
12. Central Bureau of Statistics. Population monograph of Nepal. Volumes I and II. Kathmandu:2003.
13. Department of Health Services. Annual Report 2058/59 BS (2001/2002 AD). Kathmandu: 2003.
14. Bajracharya S, Pandey S, Shakya YL. Drug prescribing pattern and disease pattern in KMC Duwakot health center. Kathmandu University Medical Journal 2004; 2:35-42.
15. World Health Organization. Scaling up the response to infectious diseases - A way out of poverty. Report on infectious diseases 2002. WHO/CDS/2002.7. Geneva: 2002.
16. INRUD, Nepal. 18th National training course on rational use of drugs. 15-20 April 2005. Kathmandu: 2005.
17. Chukwuani CM, Onifade M, Sumonu K. Survey of drug use practices and antibiotic prescribing pattern at a general hospital in Nigeria. Pharm World Sci 2002; 24:188-195.
18. Pavin M, Nurgozhin T, Hafner G, Yusufy F, Laing R. Prescribing practices of rural primary health care physicians in Uzbekistan. Trop Med Int Health 2003; 8:182-190.
19. Rishi RK, Sangeeta A, Surendra K, Tailang M. Prescription audit: experiences in Garhwal (Uttaranchal), India. Trop Doct 2003; 33:76-79.
20. Shankar R, Kumar P, Rana M, Dubey A, Shenoy N. A comparative study of drug utilization at different levels of the primary health care system in Kaski district, Western Nepal. N Z Med J 2003: 116.
21. Orrett FA. Antimicrobial prescribing patterns at a rural hospital in Trinidad: evidence for intervention measures. Afr J Med Sci 2001; 30:161-164.
22. World Health Organization. WHO global strategy for containment of antimicrobial resistance. WHO/CDS/CSR/DRS/2001.2. Geneva: 2001.

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REVIEW ARTICLE

The pathophysiology of ischemic injury to developing white matter

James J. P. Alix*

INTRODUCTION

Ischemic injury to developing white matter (WM) is of considerable clinical interest. Although the immature central nervous system (CNS) is generally regarded to be more resistant than the adult CNS to such insults, it is now known that an ischemic episode between 23 and 32 weeks gestation can result in a remarkably selective pattern of injury to the periventricular WM (1-3). In the United States, approximately 57,000 low birthweight infants (<1500 g) are born each year and while recent advances in neonatal medicine mean that around 90% of these patients survive, sadly 10% show signs of cerebral palsy of which injury to the periventricular WM is the most common neuropathological correlate (4). In addition, recent estimates suggest that a cerebrovascular event occurs in around 1 in 4000 term births, although many more cases may go unrecognised, further illustrating the enormous problem ischemic injury to the developing brain poses to clinicians (5, 6).

This pattern of pathology was first noted by the great Russian academic Virchow in 1867 (7). A century later, it was termed periventricular leukomalacia (PVL) by Banker and Larrouche when describing "necrosis of the white matter dorsal and lateral to the external angles of the lateral ventricles" (8). PVL is now considered to consist of two main components: a focal site of injury characterised by necrosis of all cell types present and a diffuse pattern of injury which appears to affect only developing oligodendroglia leading to marked hypomyelination (9). It was traditionally thought that the lesion was entirely ischaemic in origin, although numerous reports now suggest an infective/inflammatory contribution (10,11). The vulnerability of the developing human brain to ischaemia has been replicated in numerous models including mid-to-late gestation sheep, 1 day old piglets and 5 to 7 day old rats (1,12-15). This has led to an intensive investigation of the physiology behind a pathology now acknowledged to be the leading cause of neurological disability in infants surviving neonatal intensive care (9,16). This review will focus on the effects of ischemia upon developing WM, exploring the reasons behind the sensitivity of the tissue and the experimental data on the response of the constituent cell types to energy deprivation.

WHY IS IMMATURE WHITE MATTER SO VULNERABLE TO ISCHEMIA?

Cessation of blood flow to the brain results in a rapid drop in ATP levels and consequently a loss in ionic homeostasis. The majority of the energy consumed by the CNS is used to power the Na^+-K^+ ATPase, which maintains a high concentration of Na^+ outside the cell and a relatively high K^+ concentration within the cell (17). The concentration gradients of these two ions are then utilised by a range of transporters to maintain the concentration gradients of other ions, for example, Ca^{2+} via the Na^+-Ca^{2+} exchange protein. In the event of energy deprivation, the Na^+-K^+ ATPase fails leading to a rise in extracellular K^+ concentration, membrane depolarisation and the opening or reversal of numerous voltage sensitive ion channels or electrogenic transporters respectively. But why should the brain of the pre-term infant be deprived of energy?

VASCULAR ANATOMY AND PHYSIOLOGY OF CEREBRAL WHITE MATTER

The vascular biology of developing periventricular WM appears to contribute to the predisposition of the

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area to ischemic injury for several reasons: blood to the periventricular WM is supplied by long and short penetrating arteries, which branch from the middle cerebral artery (18). Even towards the end of gestation this vasculature is not fully developed; both the long and short penetrating arteries are relatively few in number with few branches (18). Thus the arterial end zones are quite some distance from the periventricular region, which may lead to severe ischemia should cerebral blood flow decline.

To compound this issue, cerebral WM receives a relatively low blood flow during development: at 1.6 to 3 mL 100g-1 min-1 just 25% of that of cortical grey matter and less than half of the accepted value for cell viability in the adult brain (19-22). Such a low level of flow means that the margin by which blood flow can fall before injury occurs is very small. A limited vasodilatory capacity, i.e. the ability of the vasculature to dilate or constrict depending upon changes in blood pressure, has also been reported in premature infants (9). One study reported a four fold increase in the risk of PVL following identification of a "pressure-passive" cerebral circulation further illustrating the potential for vascular disturbances to cause serious injury in this region (23).

OLIGODENDROGLIAL INJURY

The most common neuropathological feature of ischemic injury to the periventricular WM is the diffuse injury of the oligodendroglial population and subsequent hypomyelination (24, 25). By defining the oligodendrocyte lineage in terms of the surface antigens expressed, the populating oligodendroglia present during the time of peak vulnerability in human cerebral WM have been identified as late oligodendrocyte progenitors or oligodendrocyte precursor cells (OPCs) (26). Many studies before and since have been able to demonstrate a remarkable sensitivity of these actively differentiating cells to ischaemic and oxidative stresses, resulting in the description of maturation-dependant characteristics which may be of crucial importance in the pathogenesis of ischemic injury (1,27-29).

Glutamate, the most abundant neurotransmitter in the brain, has been shown to play an important role in the pathophysiology of OPC death. During ischaemia, extracellular glutamate levels rise dramatically and elevated glutamate levels have been observed in both animal models and clinically (30,31). When this happens both non-NMDA and NMDA receptors are over-activated (excitotoxicity), leading to a toxic Ca^{2+} flux in to the cell causing OPC damage and death (28-33). NMDA receptors have only recently been demonstrated in both neonatal and mature oligodendrocytes (32-35), while the expression of non-NMDA receptors in OPCs has been known for some time and shown to coincide with the window of vulnerability to ischaemia (12, 28, 36). Intriguingly, both the NMDA and non-NMDA receptors expressed in developing WM display curious alterations in their physiology which may contribute to the intrinsic susceptibility of the tissue. Oligodendrocyte NMDA receptors show only a weak voltage dependant block by Mg^{2+} compared with the classically described neuronal receptor. This means that these receptors permit a greater Ca^{2+} current than one might expect under the conditions of glutamate release and membrane depolarisation experienced during ischemia (32). In addition, AMPA/Kainate receptors expressed in developing oligodendroglia show reduced expression of the GluR2 subunit and so exhibit an increased permeability to Ca^{2+} (37-40). Remarkably, expression of this subunit has even been shown to be down-regulated following oxygen-glucose deprivation (OGD) preconditioning in an in vitro model (28).

While the protective effects of specific antagonists to glutamate receptors has been confirmed in vitro, situ and vivo (29, 32-34), the use of such drugs clinically is currently prevented by intolerable side-effects. These include renal toxicity due to poor water solubility in the case of AMPA receptor antagonists and behavioural effects due interference with synaptic function for NMDA receptor antagonists (41-43). Recent work, however, has revealed that these receptors may yet prove to be viable therapeutic targets as the use of the anti-convulsant topiramate has been shown to attenuate selective WM damage in a rodent model of WM injury (12). Xenon, a non-toxic anaesthetic gas that reduces neurotransmitter release and antagonizes NMDA receptors, has also been shown to provide significant neuro-protection in neonatal rats (44). In addition, the unusual subunit composition of oligodendrocyte NMDA receptors offers the potential of a novel drug target away from synaptic receptors (32, 33). In a recent article on this subject it was noted that these receptors contain the NR3 subunit, which is responsible for the decreased Mg^{2+} block seen in WM NMDA receptors (45). Currently, there are no selective agonists or antagonists for this subunit and Lipton suggests the development of such drugs may be of great importance for future clinical interventions (45).

There are many potential sources for glutamate release during ischemia. Release from axons is one possibility and glutamate release/depletion during ischaemia has been reported in optic nerve and spinal cord models (35, 46). This liberation could potentially occur via the reversal of electrogenic Na^{+}-dependant glutamate transporters due to the conditions of ischemia. For example, membrane depolarisation and a

concurrent increase in intracellular Na^+, due to an inactivating Na^+ conductance, was suggested in the spinal cord study (46) while release following axonal disruption is another possibility. The release of glutamate from astrocytes, following cell death and clasmatodendrosis (loss of cell processes), has also been suggested (47). In a companion paper, prevention of Na^+-K^+-Cl^- co-transporter (NKCC) mediated astrocyte swelling neatly prevented non-NMDA receptor mediated rises in intracellular Ca^{2+} in neighbouring oligodendroglia during OGD, indicating a potential role for swelling mediated glutamate release (35). As well as receptor-mediated glutamate cell death, a non-receptor mediated affect may also operate in oligodendrocytes. Activation of a glutamate-cystine exchanger can lead to a reduction in cellular levels of cystine and hence decreased synthesis of the important antioxidant glutathione (48). This leaves the cell vulnerable to free radical attack, another weakness of OPCs.

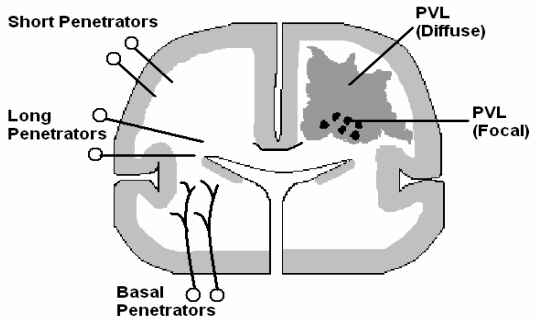

Figure 1. Coronal section of cerebrum. The focal (black circles) and diffuse (grey shading) components of PVL are shown in one hemisphere and the cerebral vascular supply in the other. The long and short penetrating arteries supply the cerebral WM, as shown. From (9).

That ischemia and reperfusion lead to the generation of free radicals is well established and OPCs have been demonstrated to be highly vulnerable to these species compared to mature oligodendrocytes (27,48,49). Cystine deprivation has been used to demonstrate the sensitivity of OPCs to oxidative stress caused by ensuing glutathione exhaustion, a treatment which has no effect upon the viability of mature oligodendrocytes (27,50). The exact nature of the discrepancy between the two developmental stages still requires further investigation but may be the result of a developmental delay in the maturity of anti-oxidant defences such as glutathione peroxidase and/or catalase (9). Volpe suggests that, should these defences be overwhelmed, hydrogen peroxide accumulates and combines with Fe^{2+} accumulated during differentiation. This may then lead, via the Fenton reaction, to the production of hydroxyl ions and cell death (9). Although devastating

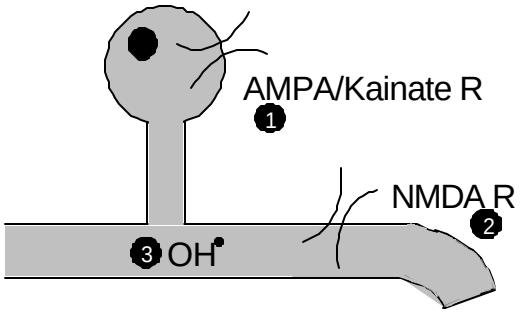

Figure 2. Oligodendrocyte injury during ischemia. Rising levels of glutamate over stimulate both NMDA and non-NMDA receptors leading to a toxic influx of Ca (1 & 2). In addition, a developmental lag in anti-oxidant defences can lead to the build up of lethal free radicals such as the hydroxyl radical (3).

in effect this mode of injury is potentially the most treatable via clinically safe anti-oxidants such as vitamin E, which have the ability to rescue OPCs from free radical mediated death (Volpe unpublished data). Encouragingly, the phase III Stroke-Acute Ischemic NXY treatment trial (SAINT 1) provided evidence that NXY-059, a free-radical-trapping agent that has been neuroprotective in animal models, may be an effective adjunct to tissue plasminogen activator in the acute setting (51).

ASTROCYTES AND ISCHEMIA

Astrocytes are the most numerous cell type of the central nervous system but there is little information on their mechanism(s) of ischemic injury. Potential reasons for this include their relatively high resistance to energy deprivation and the difficulty of studying cell viability in vivo (52,53). Thus, most studies describing astrocyte pathophysiology have used cell culture methods to do so and significant differences, such as an attenuated rise in intracellular Ca^{2+} concentration in vitro when compared to in situ preparations, have been noted (52-54). Pooled studies on the response of astrocytes to ischemia have generated several potential causes of injury such as Ca^{2+} influx through L-type Ca^{2+} channels and Na^+-Ca^{2+} exchange reversal, release from internal stores and cell swelling (47,52,54-57). Importantly, rapid astrocyte injury has been reported after hypoxia-ischemia in the neonatal striatum justifying investigations into astrocyte death in the immature brain (58).

With regard to the developing brain only two of the above studies attempted to use astrocytes in an immature in situ environment. The first of these used the rat optic nerve (RON) from animals aged between post-natal day 0-2, time points prior to the migration of oligodendroglia into the tract (52). The author was therefore able to study the response of in situ astrocytes

to ischaemia by loading the Ca^{2+} dye FURA-2 into the whole optic nerve. The key findings of the paper were a toxic Ca^{2+} influx mediated by T- and L-type Ca^{2+} channels and a protective role for the Na^{+}-Ca^{2+} exchanger. However, the P0-2 RON is more immature than the WM affected in human patients (1, 26). When similar experiments were performed using the P8-12 RON, in which myelination is just underway (a feature of the perinatal WM injured by ischemia), a different mechanism of injury was found (47). In this paper removal of extracellular Ca^{2+} was not protective (in fact it increased cell death), while removal of Na^{2+} Cl^{-} or block of the NKCC with bumetanide was, suggesting cell swelling may be an important factor in cell death. Interestingly, analysis of volume changes during ischaemia did not reveal any changes although in experiments repeated in the absence of Ca^{2+}, significant swelling was observed. The authors concluded that ischaemia poses an osmo-regulatory challenge meditated by the NKCC and controlled by Ca^{2+}-dependant mechanisms but this does not prevent cell death; the actual cause of cell death was not resolved (53). Future studies utilising recent advances in molecular biology may prove more successful in this respect. For example, the availability of transgenic mice generated by the laboratory of Dr. V Gallo at the Children's National Medical Centre, Washington DC, in which green fluorescent protein expression is under the control of the astrocyte specific GFAP promoter, should provide investigators with the means of assessing astrocyte injury more thoroughly in an in situ environment.

Astrocytes have long been ascribed a housekeeping function and ischaemia-induced alterations of the many functions they perform are capable of influencing the outcome of surrounding cells. For example, numerous studies of energy deprivation in the perinatal brain have reported astrocytic activation (59-62). Astrocytes may become "activated" by inflammatory mediators in a range of circumstances such as ischaemia and trauma leading to a characteristic up-regulation of GFAP, cellular hypertrophy, astrocyte proliferation and process extension (63). The consequences of astrocytic activation are not well understood and may be both beneficial and detrimental. For example, free radicals and inflammatory mediators such as TNFa may be released with the potential to cause injury while trophic factors such as TGFd and brain derived neurotrophic factor are also released and, remarkably, free radical scavenging is possible (64-69). In addition, astrocytes may affect the outcome of neighbouring cells through impaired K+ and glutamate uptake (70,71), further illustrating the potential importance of astrocyte protection.

AXON DAMAGE DURING ISCHEMIA

Banker and Larroche's (1962) description of PVL noted the presence of "retraction balls and clubs", that is, the presence of swollen axon cylinders and such injury will undoubtedly contribute to the phenotype of the ensuing disorder. Recently amyloid precursor protein, a marker of the integrity of fast axonal transport and therefore axon injury, has been detected in the brains of infants with WM injury (59, 72-74). Furthermore, in a developmental study on axon conduction during acute energy deprivation, a rapid decrease in the ability of RONs to recover electrical activity following OGD was noted around the onset of myelination (75).

Although papers on the mechanisms of injury to myelinating axons have not been forthcoming, the response of myelinated central axons to energy deprivation has been extensively studied, primarily using the hypoxic rat optic nerve model (76-78). Initial investigations revealed that a toxic Ca^{2+} influx was mediated via reversal of the Na^{+}-Ca^{2+} exchange protein following a rise in intra-axonal Na+ concentration (77). This Na^{+} loading, caused by non-inactivating Na+ channels, coupled with anoxia induced membrane depolarisation drives the electrogenic Na^{+}-Ca^{2+} exchange protein into reverse operation with catastrophic consequences for axon function (79). Some later studies also found a protective role for specific voltage gated Ca^{2+} channel antagonists (78, 80).

Following on from these initial studies, investigators are now beginning to look at the mechanisms behind the injury sustained following both oxygen and glucose withdrawal; perhaps a more clinically relevant model given that the cessation of blood flow that occurs during stroke will decrease the availability of both oxygen and glucose. Using an acute brain slice preparation Tekkök and Goldberg reported AMPA/Kainate receptor mediated oligodendrocyte death in line with previous studies, but also used stimulus-evoked compound action potentials and immunohistochemistry to assess axon integrity (81). While Ca^{2+} removal preserved axon function following an insult, block of the Na^{+}-Ca^{2+} exchange, in contrast to anoxia studies, provided only partial protection. Far more effective in preserving both compound action potential (CAP) conduction and neurofilament immunofluorescence was AMPA/Kainate blockade, a result which was not attributable to the protection of neuronal somata. The authors speculated that the underlying reasons for this might include myelin damage, an increase in tissue energy use or the loss of trophic support (81). Similar protection of optic nerve axons following OGD withdrawal has been reported in abstract form raising

the possibility that in the event of a more severe metabolic insult, excitotoxicity may play an important role in acute axonal injury (82, 83).

Simulated ischemia has also led to reports of the "Trojan horse" of intra-axonal Ca^{2+} release" (84). Ouardouz et al. demonstrated that in rat dorsal columns, removal of bath Ca^{2+} did not improve post-ischemic

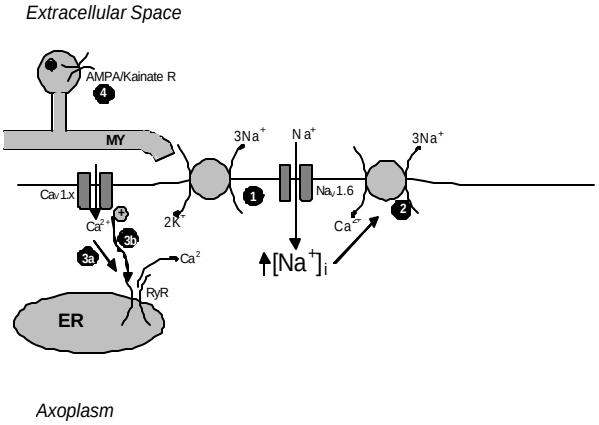

Figure 3. Diagram illustrating mechanisms of ischemic injury to CNS axons. Following failure of the Na^+-K^+ pump Na+ accumulates in the axoplasm via a non-inactivating Na^+ conductance (1). This increase results in reversal of the membrane Na^+-Ca^{2+} exchanger (2). Ca^{2+} influx mediated by voltage gated Ca2+ channels may activate ER ryanodine receptors through either Ca^{2+}-induced or depolarisation coupled means (3a & b). Finally, over activation of AMPA/Kainate receptors on oligodendroglia (4) might also contribute to the loss of functional integrity of the axon.

CAP recovery and Ca^{2+} imaging experiments revealed that a rise in intracellular Ca^{2+} still persisted in such experiments (85). Ryanodine or blockers of the L-type Ca^{2+} channel voltage sensor (such as diltiazem) were protective during zero Ca^{2+} experiments. Subsequent immunoprecipitation and immunohistochemical studies revealed an association between L-type Ca^{2+} channels and ryanodine receptors on axons. These data led the authors to describe a mechanism similar to the excitation-contraction coupling seen in skeletal muscle where ischemic depolarisation sensed by L-type VGCCs activates ryanodine receptors on the endoplasmic reticulum (ER) leading to the release of damaging amounts of Ca^{2+}. Such evidence indicates that ischemia-induced axon injury in the developing brain is likely to be the result of numerous pathways operating together leading to a catastrophic loss of function.

CONCLUSION

Although the developing brain is relatively resistant to ischemia, severe insults can result in a characteristically cortical-sparring pathology associated with both mental and physical disability. Numerous models for studying the effects of energy deprivation upon the developing brain are now available and have resulted in an ever growing body of literature on the subject. An understanding of the Byzantine pathophysiology of ischemia-induced white matter injury is steadily leading researchers towards the development of effective therapeutic interventions in the near future.

REFERENCES

1. Back, S.A., B.H. Han, N.L. Luo, et al. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. J Neurosci 2002; 22(2): 455-63.
2. Duffy, T.E., Kohle, S.J., and Vannucci, R.C. Carbohydrate and energy metabolism in perinatal rat brain: relation to survival in anoxia. J Neurochem 1940; 24(2): 271-276.
3. Kabat, H. The greater resistance of very young animals to arrest of the brain circulation. Am. J. Physiol 1940; 130: 588-599.
4. Volpe, J.J. Neurobiology of periventricular leukomalacia in the premature infant. Pediatr Res 2001; 50(5): 553-62.
5. Lynch, J.K., D.G. Hirtz, G. DeVeber, and K.B. Nelson. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics 2002; 109(1): 116-23.
6. Lynch, J.K. and K.B. Nelson. Epidemiology of perinatal stroke. Curr Opin Pediatr 2001; 13(6): 499-505.
7. Virchow, R. Zur pathologischen Anatomie des Gehirns I. Congenitale Encephalitis und Myelitis. (In German). Virchows Arch Pathol Anat 1867; 38: 129-142.
8. Banker, B.Q. and J.C. Larroche. Periventricular leukomalacia of infancy. A form of neonatal anoxic encephalopathy. Arch Neurol 1962; 7: 386-410.
9. Volpe, J.J., Neurology of the Newborn. 2001: WB Saunders Company.
10. Leviton, A., N. Paneth, M.L. Reuss, et al. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Developmental Epidemiology Network Investigators. Pediatr Res 1999; 46(5): 566-75.
11. Wu, Y.W. and J.M. Colford, Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. JAMA 2000; 284(11): 1417-24.
12. Follett, P.L., P.A. Rosenberg, J.J. Volpe, and F.E. Jensen. NBQX attenuates excitotoxic injury in developing white matter. J Neurosci 2000; 20(24): 9235-41.
13. Rees, S., M. Stringer, Y. Just, S.B. Hooper, and R. Harding. The vulnerability of the fetal sheep brain to hypoxemia at mid-gestation. Brain Res Dev Brain Res 1997; 103(2): 103-18.
14. Vannucci, R.C., J.R. Connor, D.T. Mauger, et al. Rat model of perinatal hypoxic-ischemic brain damage. J Neurosci Res 1999; 55(2): 158-63.
15. Yue, X., H. Mehmet, J. Penrice, et al. Apoptosis and necrosis in the newborn piglet brain following transient cerebral hypoxia-ischaemia. Neuropathol Appl Neurobiol 1997; 23(1): 16-25.
16. Back, S.A. and S.A. Rivkees. Emerging concepts in periventricular white matter injury. Semin Perinatol 2004; 28(6): 405-14.
17. Astrup, J., P.M. Sorensen, and H.R. Sorensen. Oxygen and glucose consumption related to Na+-K+ transport in canine brain. Stroke 1981; 12(6): 726-30.
18. Rorke, L.B. Anatomical features of the developing brain implicated in pathogenesis of hypoxic-ischemic injury. Brain Pathol 1992; 2(3): 211-21.
19. Altman, D.I., W.J. Powers, J.M. Perlman, P. Herscovitch, S.L.

Volpe, and J.J. Volpe. Cerebral blood flow requirement for brain viability in newborn infants is lower than in adults. Ann Neurol 1988; 24(2): 218-26.
20. Greisen, G. and K. Borch. White matter injury in the preterm neonate: the role of perfusion. Dev Neurosci 2001; 23(3): 209-12.
21. Borch, K. and G. Greisen. Blood flow distribution in the normal human preterm brain. Pediatr Res 1998; 43(1): 28-33.
22. Powers, W.J., R.L. Grubb, Jr., D. Darriet, and M.E. Raichle. Cerebral blood flow and cerebral metabolic rate of oxygen requirements for cerebral function and viability in humans. J Cereb Blood Flow Metab 1985; 5(4): 600-8.
23. Tsuji, M., J.P. Saul, A. du Plessis, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. Pediatrics 2000; 106(4): 625-32.
24. Iida, K., S. Takashima, and K. Ueda. Immunohistochemical study of myelination and oligodendrocyte in infants with periventricular leukomalacia. Pediatr Neurol 1995; 13(4): 296-304.
25. Paneth, N., R. Rudelli, W. Monte, et al. White matter necrosis in very low birth weight infants: neuropathologic and ultrasonographic findings in infants surviving six days or longer. J Pediatr 1990; 116(6): 975-84.
26. Back, S.A., N.L. Luo, N.S. Borenstein, J.M. Levine, J.J. Volpe, and H.C. Kinney. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci 2001; 21(4): 1302-12.
27. Back, S.A., X. Gan, Y. Li, P.A. Rosenberg, and J.J. Volpe. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. J Neurosci 1998; 18(16): 6241-53.
28. Deng, W., P.A. Rosenberg, J.J. Volpe, and F.E. Jensen. Calcium-permeable AMPA/kainate receptors mediate toxicity and preconditioning by oxygen-glucose deprivation in oligodendrocyte precursors. Proc Natl Acad Sci USA 2003; 100(11): 6801-6.
29. Fern, R. and T. Moller. Rapid ischemic cell death in immature oligodendrocytes: a fatal glutamate release feedback loop. J Neurosci 2000; 20(1): 34-42.
30. Hagberg, H. Hypoxic-ischemic damage in the neonatal brain: excitatory amino acids. Dev Pharmacol Ther 1992; 18(3-4): 139-44.
31. Silverstein, F.S., B. Naik, and J. Simpson. Hypoxia-ischemia stimulates hippocampal glutamate efflux in perinatal rat brain: an in vivo microdialysis study. Pediatr Res 1991; 30(6): 587-90.
32. Karadottir, R., P. Cavelier, L.H. Bergersen, and D. Attwell. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. Nature 2005; 438(7071): 1162-6.
33. Salter, M.G. and R. Fern. NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. Nature 2005; 438(7071): 1167-71.
34. Micu, I., Q. Jiang, E. Coderre, et al. NMDA receptors mediate calcium accumulation in myelin during chemical ischaemia. Nature 2005; 439(7079): 988-92.
35. Wilke, S., R. Thomas, N. Allcock, and R. Fern. Mechanism of acute ischemic injury of oligodendroglia in early myelinating white matter: the importance of astrocyte injury and glutamate release. J Neuropathol Exp Neurol 2004; 63(8): 872-81.
36. Rosenberg, P.A., W. Dai, X.D. Gan, et al. Mature myelin basic protein-expressing oligodendrocytes are insensitive to kainate toxicity. J Neurosci Res 2003; 71(2): 237-45.
37. Burnashev, N., H. Monyer, P.H. Seeburg, and B. Sakmann. Divalent ion permeability of AMPA receptor channels is dominated by the edited form of a single subunit. Neuron 1992; 8(1): 189-98.
38. Durand, G.M. and R.S. Zukin. Developmental regulation of mRNAs encoding rat brain kainate/AMPA receptors: a northern analysis study. J Neurochem 1993; 61(6): 2239-46.
39. Monyer, H., N. Burnashev, D.J. Laurie, B. Sakmann, and P.H. Seeburg. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron 1994; 12(3): 529-40.
40. Pellegrini-Giampietro, D.E., M.V. Bennett, and R.S. Zukin. Are Ca(2+)-permeable kainate/AMPA receptors more abundant in immature brain? Neurosci Lett 1992; 144(1-2): 65-9.
41. Akins, P.T. and R.P. Atkinson. Glutamate AMPA receptor antagonist treatment for ischaemic stroke. Curr Med Res Opin 2002; 18 Suppl 2: s9-13.
42. Ikonomidou, C. and L. Turski. Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol 2002; 1(6): 383-6.
43. Low, S.J. and C.L. Roland. Review of NMDA antagonist-induced neurotoxicity and implications for clinical development. Int J Clin Pharmacol Ther 2004; 42(1): 1-14.
44. Dingley, J., J. Tooley, H. Porter, and M. Thoresen. Xenon Provides Short-Term Neuroprotection in Neonatal Rats When Administered After Hypoxia-Ischemia. Stroke, 2005.
45. Lipton, S.A. NMDA receptors, glial cells, and clinical medicine. Neuron 2006; 50(1): 9-11.
46. Li, S. and P.K. Stys. $Na(^{+})$-$K(^{+})$-ATPase inhibition and depolarization induce glutamate release via reverse Na(+)-dependent transport in spinal cord white matter. Neuroscience 2001; 107(4): 675-83.
47. Thomas, R., M.G. Salter, S. Wilke, et al. Acute ischemic injury of astrocytes is mediated by Na-K-Cl cotransport and not Ca2+ influx at a key point in white matter development. J Neuropathol Exp Neurol 2004; 63(8): 856-71.
48. Oka, A., M.J. Belliveau, P.A. Rosenberg, and J.J. Volpe. Vulnerability of oligodendroglia to glutamate: pharmacology, mechanisms, and prevention. J Neurosci 1993; 13(4): 1441-53.
49. Fellman, V. and K.O. Raivio. Reperfusion injury as the mechanism of brain damage after perinatal asphyxia. Pediatr Res 1997; 41(5): 599-606.
50. Yonezawa, M., S.A. Back, X. Gan, P.A. Rosenberg, and J.J. Volpe. Cystine deprivation induces oligodendroglial death: rescue by free radical scavengers and by a diffusible glial factor. J Neurochem 1996; 67(2): 566-73.
51. Lees, K.R., J.A. Zivin, T. Ashwood, et al. NXY-059 for acute ischemic stroke. N Engl J Med 2006; 354(6): 588-600.
52. Fern, R. Intracellular calcium and cell death during ischemia in neonatal rat white matter astrocytes in situ. J Neurosci 1998; 18(18): 7232-43.
53. Goldberg, M.P. and D.W. Choi. Combined oxygen and glucose deprivation in cortical cell culture: calcium-dependent and calcium-independent mechanisms of neuronal injury. J Neurosci 1993; 13(8): 3510-24.
54. Duffy, S. and B.A. MacVicar. In vitro ischemia promotes calcium influx and intracellular calcium release in hippocampal astrocytes. J Neurosci 1996; 16(1): 71-81.
55. Bondarenko, A., N. Svichar, and M. Chesler. Role of Na+-H+ and Na+-Ca2+ exchange in hypoxia-related acute astrocyte death. Glia 2005; 49(1): 143-52.
56. Holgado, A. and L. Beauge. The Na(+)-Ca2+ exchange system in rat glial cells in culture: activation by external monovalent cations. Glia 1995; 14(2): 77-86.
57. MacVicar, B.A. Voltage-dependent calcium channels in glial cells. Science 1984; 226(4680): 1345-7.
58. Martin, L.J., A.M. Brambrink, C. Lehmann, et al. Hypoxia-ischemia causes abnormalities in glutamate transporters and death of astroglia and neurons in newborn striatum. Ann Neurol 1997; 42(3): 335-48.
59. Deguchi, K., K. Oguchi, and S. Takashima. Characteristic

neuropathology of leukomalacia in extremely low birth weight infants. Pediatr Neurol 1997; 16(4): 296-300.
60. Farkas, E., A. Institoris, F. Domoki, A. Mihaly, P.G. Luiten, and F. Bari. Diazoxide and dimethyl sulphoxide prevent cerebral hypoperfusion-related learning dysfunction and brain damage after carotid artery occlusion. Brain Res 2004; 1008(2): 252-60.
61. Haynes, R.L., R.D. Folkerth, R.J. Keefe, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. J Neuropathol Exp Neurol 2003; 62(5): 441-50.
62. Sizonenko, S.V., J.Z. Kiss, T. Inder, P.D. Gluckman, and C.E. Williams. Distinctive neuropathologic alterations in the deep layers of the parietal cortex after moderate ischemic-hypoxic injury in the P3 immature rat brain. Pediatr Res 2005; 57(6): 865-72.
63. Ridet, J.L., S.K. Malhotra, A. Privat, and F.H. Gage. Reactive astrocytes: cellular and molecular cues to biological function. Trends Neurosci 1997; 20(12): 570-7.
64. Bruno, V., G. Battaglia, G. Casabona, A. Copani, F. Caciagli, and F. Nicoletti. Neuroprotection by glial metabotropic glutamate receptors is mediated by transforming growth factor-beta. J Neurosci 1998; 18(23): 9594-600.
65. Dhandapani, K.M., M. Hadman, L. De Sevilla, M.F. Wade, V.B. Mahesh, and D.W. Brann. Astrocyte protection of neurons: role of transforming growth factor-beta signaling via a c-Jun-AP-1 protective pathway. J Biol Chem 2003; 278(44): 43329-39.
66. D'Souza, S.D., K.A. Alinauskas, and J.P. Antel. Ciliary neurotrophic factor selectively protects human oligodendrocytes from tumor necrosis factor-mediated injury. J Neurosci Res 1996; 43(3): 289-98.
67. Iwata-Ichikawa, E., Y. Kondo, I. Miyazaki, M. Asanuma, and N. Ogawa. Glial cells protect neurons against oxidative stress via transcriptional up-regulation of the glutathione synthesis. J Neurochem 1999; 72(6): 2334-44.
68. Lucius, R. and J. Sievers. Postnatal retinal ganglion cells in vitro: protection against reactive oxygen species (ROS)-induced axonal degeneration by cocultured astrocytes. Brain Res 1996; 743(1-2): 56-62.
69. Trendelenburg, G. and U. Dirnagl. Neuroprotective role of astrocytes in cerebral ischemia: focus on ischemic preconditioning. Glia 2005; 50(4): 307-20.
70. Matute, C., M. Domercq, and M.V. Sanchez-Gomez. Glutamate-mediated glial injury: mechanisms and clinical importance. Glia 2006; 53(2): 212-24.
71. Ransom, B.R. and R.K. Orkand. Glial-neuronal interactions in non-synaptic areas of the brain: studies in the optic nerve. Trends Neurosci 1996; 19(8): 352-8.
72. Arai, Y., K. Deguchi, M. Mizuguchi, and S. Takashima. Expression of beta-amyloid precursor protein in axons of periventricular leukomalacia brains. Pediatr Neurol 1995; 13(2): 161-3.
73. Meng, S.Z., Y. Arai, K. Deguchi, and S. Takashima. Early detection of axonal and neuronal lesions in prenatal-onset periventricular leukomalacia. Brain Dev 1997; 19(7): 480-4.
74. Ohyu, J., G. Marumo, H. Ozawa, et al. Early axonal and glial pathology in fetal sheep brains with leukomalacia induced by repeated umbilical cord occlusion. Brain Dev 1999; 21(4): 248-52.
75. Fern, R., P. Davis, S.G. Waxman, and B.R. Ransom. Axon conduction and survival in CNS white matter during energy deprivation: a developmental study. J Neurophysiol 1998; 79(1): 95-105.
76. Stys, P.K., B.R. Ransom, S.G. Waxman, and P.K. Davis. Role of extracellular calcium in anoxic injury of mammalian central white matter. Proc Natl Acad Sci USA 1990; 87(11): 4212-6.
77. Stys, P.K., S.G. Waxman, and B.R. Ransom. Ionic mechanisms of anoxic injury in mammalian CNS white matter: role of Na+ channels and $Na(^{+})$-Ca^{2+} exchanger. J Neurosci 1992; 12(2): 430-9.
78. Fern, R., B.R. Ransom, and S.G. Waxman. Voltage-gated calcium channels in CNS white matter: role in anoxic injury. J Neurophysiol 1995; 74(1): 369-77.
79. Leppanen, L. and P.K. Stys. Ion transport and membrane potential in CNS myelinated axons. II. Effects of metabolic inhibition. J Neurophysiol 1997; 78(4): 2095-107.
80. Brown, A.M., R.E. Westenbroek, W.A. Catterall, and B.R. Ransom. Axonal L-type Ca^{2+} channels and anoxic injury in rat CNS white matter. J Neurophysiol 2001; 85(2): 900-11.
81. Tekkok, S.B. and M.P. Goldberg. Ampa/kainate receptor activation mediates hypoxic oligodendrocyte death and axonal injury in cerebral white matter. J Neurosci 2001; 21(12): 4237-48.
82. Tekkok SB, B.E.a.R.B. Older adult animals and the mechanisms of ischemic white matter injury. Program No. 100.12. 2005 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2005.
83. B.R. Ransom, S.B.T. Perceptor pharmacology of excitotoxic injury in mouse optic nerve. in Program No. 100.13. 2005 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2005. 2005.
84. Ransom, B.R. and A.M. Brown. Intracellular Ca2+ release and ischemic axon injury: the Trojan horse is back. Neuron 2003; 40(1): 2-4.
85. Ouardouz, M., M.A. Nikolaeva, E. Coderre, et al. Depolarization-induced Ca2+ release in ischemic spinal cord white matter involves L-type Ca^{2+} channel activation of ryanodine receptors. Neuron 2003; 40(1): 53-63.

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REVIEW ARTICLE

An overview of intracranial aneurysms

Alexander Keedy*

ABSTRACT Intracranial aneurysms are relatively common, with a prevalence of approximately 4%. Unruptured aneurysms may cause symptoms mainly due to a mass effect, but the real danger is when an aneurysm ruptures, leading to a subarachnoid hemorrhage. Most aneurysms are asymptomatic and will not rupture, but they grow unpredictably and even small aneurysms carry a risk of rupture. Intracranial aneurysms are diagnosed and monitored with imaging including intra-arterial digital subtraction angiography, computed tomography angiography, magnetic resonance angiography, and recently transcranial Doppler ultrasonograpy has been proposed as a potential modality. Treatment options include observation, endovascular coiling, and surgical clipping. This paper will review the epidemiology, pathogenesis, clinical presentation, diagnosis, natural history, and management of unruptured saccular intracranial aneurysms.

INTRODUCTION

Aneurysms of the cerebral vasculature are relatively common. A recent systematic review collecting data from many countries reported a prevalence of 0.4% and 3.6% in retrospective and prospective autopsy studies, respectively, and 3.7% and 6.0% in retrospective and prospective angiographic studies, respectively (1). The angiographic studies likely overestimate the true prevalence due to a selection bias, whereas the retrospective autopsy studies likely underestimate the true prevalence due to an inability to review the original material. Eighty-five percent of saccular aneurysms of the cerebral vasculature occur in the circle of Willis (2). Multiple aneurysms are seen in 30% of patients. Most are small and asymptomatic, but each year, approximately 30,000 people in the United States suffer a rupture, peaking in the sixth decade (3). When an intracranial aneurysm ruptures, it may bleed into the brain parenchyma resulting in a parenchymal hemorrhage, or more often, it will bleed into the subarachnoid space, resulting in a subarachnoid hemorrhage (SAH). A SAH is a catastrophic event with a mortality rate of 25% to 50%. Permanent disability occurs in nearly 50% of the survivors, thus, only approximately one-third of patients who suffer a SAH have a positive outcome (3).

RISK FACTORS

There are many risk factors for the development of intracranial aneurysms, both inherited and acquired. Females are more prone to aneurysm rupture, with SAH 1.6 times more common in women. The prevalence of aneurysms is increased in certain genetic diseases; the classic example is autosomal dominant polycystic kidney disease (ADPKD), but other diseases such as Ehlers-Danlos syndrome, neurofibromatosis, and a1-antitrypsin deficiency also demonstrate a link. In ADPKD, 10% to 15% of patients develop intracranial aneurysms. Marfan's Syndrome was once thought to be linked to intracranial aneurysm formation, but recent evidence suggests that this may not be true. Aneurysms also run in families in the absence of an identified genetic disorder, with a prevalence of 7% to 20% in first or second degree relatives of patients who have suffered a SAH (2, 3). The acquired risk factors are listed in Table 1.

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Table 1. Acquired risk factors for intracranial aneurysms (4).

Increasing age
Hypertension
Smoking
Alcohol abuse
Estrogen deficiency
Hypercholesterolemia
Carotid artery stenosis

PATHOGENESIS

There are four main types of intracranial aneurysms: saccular, fusiform, dissecting, and micotic type. The saccular type accounts for 90% of intracranial aneurysms, thus, it will be the focus of this review. Saccular aneurysms are a result of abberations to the normal arterial structure, which consists of the tunica intima adjacent to the lumen of the vessel, the tunica media (the muscular middle layer), and the tunica adventitia (the outer layer composed mainly of connective tissue). The internal elastic lamina delimits the tunica intima from the tunica media, and the external elastic lamina delimits the tunica media from the tunica adventitia. Saccular aneurysms occur when there is collagen deficiency in the internal elastic lamina and breakdown of the tunica media. An outpouching, consisting of only tunica intima and adventitia, protrudes through the defect in the internal elastic lamina and tunica media to produce the aneurismal sac (5, 6). The impaired integrity of the wall may be due to congenital weakness or absence of the tunica media or adventitia, degenerative alterations of the internal elastic lamina (from hypertension, turbulent flow, or atherosclerotic deposits in the wall), or both of these factors combined (2). Low collagen and elevated plasma elastase has been observed in patients with aneurysms, suggesting that vascular remodeling involving collagen and elastin plays an important role (4).

Eighty-five percent of saccular aneurysms arise from the arteries of the circle of Willis. The most frequent location is the anterior communicating artery (35%), followed by the internal carotid artery (30%-including the carotid artery itself, the posterior communicating artery, and the ophthalmic artery), the middle cerebral artery (22%), and finally, the posterior circulation sites, most commonly the basilar artery tip. See Figure 1 for a scheme of the circle of Willis. Multiple aneurysms are found in approximately 30% of patients (2).

CLINICAL PRESENTATION

The symptoms of SAH result from blood spilling into the cerebrospinal fluid (CSF) and the subsequent increased intracranial pressure and breakdown of blood products. Characteristic symptoms include: "the worst headache of my life," nausea and vomiting, loss of consciousness, neck stiffness, and seizures (7, 8). The clinical manifestations of unruptured aneurysms, however, are much more subtle. Only 10-15% of intracranial aneurysms are symptomatic (9, 10), with the majority being identified incidentally during evaluation for other conditions. When present, the symptoms are primarily due to the mass effect of a large aneurysm, or possibly from minimal leakage of blood which irritates the meninges, though not enough to be classified as a hemorrhage. These symptoms include headache, unilateral third cranial nerve palsy (from a posterior communicating artery aneurysm), bilateral temporal hemianopsia (from an anterior communication artery aneurysm impinging on the optic chiasm) ischemic cerebrovascular disease, poorly defined spells, and seizures (4, 11). These symptoms may be a warning sign of an impending rupture, as 10% to 43% of patients with SAH report experiencing a sentinel headache in the 2 months preceding the rupture (12).

Table 2. Comparison of Sensitivity and Specificity of CTA, MRA, and TCD in the diagnosis of intracranial aneurysms (4).

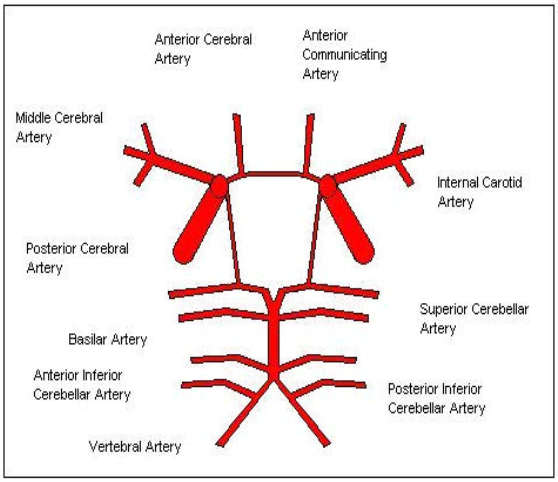

Figure 1. The circle of Willis.

Method	Sensitivity	Specificity
CTA	90	86
MRA	87	95
TCD	82	95

DIAGNOSIS AND IMAGING FINDINGS

There are currently three imaging modalities widely used in the diagnosis of intracranial aneurysms: intra-arterial digital subtraction angiography (IADSA), computed tomography angiography (CTA) and

magnetic resonance angiography (MRA). IADSA is similar to conventional angiography in that a catheter is advanced in the arterial system to the point of interest, and radio-opaque contrast material is injected while images are acquired. The contrast fills the lumen of the arteries; thus, the vessel anatomy is visualized on the image. In conventional angiography, serial x-ray films are captured, while in IADSA, serial digital images are obtained and stored on a computer. An initial image acquired before contrast injection is subtracted from the post-contrast images. The resultant image displays dark vessels against a blank background (see Figure 2). This technique allows greater contrast resolution (the areas with contrast are more obvious), but decreased spatial resolution (because digitally acquired images have a lower resolution than films) when compared with conventional angiography.

CTA is another technique of vascular imaging which involves obtaining a normal CT scan while intravenous contrast material is injected. The contrast material is radio-opaque, so it appears white on the CT image. The serial axial slices enhanced with contrast are analyzed by a computer program that forms a three-dimensional reconstruction of the vascular anatomy. The resultant image is a dynamic model that can be rotated in order to view the image from multiple perspectives (see Figure 3).

Table 3. The morbidity, mortality, and rebleeding rate of intervention for intracranial aneurysms (3, 4, 23, 28)

Outcome	Intravascular Coiling (%)	Surgical Clipping (%)
Mortality	1.0-1.1	2.6-3.8
Morbidity	3.7-4.0	10.9-12.1
Rebleeding	2.6	0-0.9

Similar to CTA, MRA is a technique which uses serial axial MRI images to form a three-dimensional representation of the vascular anatomy. Unlike CTA, however, MRA does not require the use of intravenous contrast material. This is because the signal obtained in magnetic resonance imaging depends on the magnetic properties of the area being imaged. A magnetic pulse aligns all the protons in a certain area, and measuring the amount of time necessary for those protons to return to their pre-magnetization state generates the signal which produces the MR image. With a moving substance such as blood, the protons are aligned during the magnetic pulse, but by the time the signal is collected, the aligned protons have moved out of the area which is being imaged, and new 'non-magnetized' protons have taken their place. Because these new protons have not been magnetized, a signal is not generated and the blood vessel lumen appears as a 'signal void' on the image (this is an oversimplified explanation). The lack of signal distinguishes the vessels from the surroundings (see Figure 4). In some cases, a gadolinium contrast material may be used to provide better imaging of the vessels. The advantage of MRA is that it can be used in patients who cannot tolerate the iodine based contrast used in IADSA and CTA, such as patients with allergic reactions or with renal failure.

The gold standard for diagnosis of intracranial aneurysms is currently IADSA, but a diagnosis can also be provided by CTA and MRA. The contrast provided during IADSA causes the aneurysm to appear on fluoroscopy as a radio opaque, smooth margined, saccular out-pouching of the cerebral vasculature (see Figure 2) (13). A thrombus within the aneurismal sac will be visualized as an interruption to the rounded margin because contrast material will not penetrate the clotted, stationary blood. Such a thrombus will be better delineated with CTA or MRA than IADSA, as these former modalities image the vessel wall and surroundings, not only the lumen of the vessel. On CTA, if large enough, an aneurysm will appear as a rounded, spherical mass with attenuation (whiteness) equal to that seen in the large vessels. CT may also depict calcifications in the wall of the aneurysm, or the presence of thrombus within the lumen which will not enhance with contrast medium; these characteristics are seen more frequently in giant aneurysms (>25mm) (14). On MRA, the lumen of the aneurysm will appear as a flow void, meaning that it does produce a magnetic signal because blood flow has slowed due to the larger cross-sectional area of the aneurysms compared to the nearby normal vasculature. Areas of high signal intensity surrounding the flow void area of the aneurysm on MRA likely represent a rupture with subsequent hemorrhage: the high signal pattern is produced by stagnant blood (14).

As mentioned above, the gold-standard for diagnosis of cerebral aneurysms is IADSA because it remains the test with the highest spatial resolution. But some cases are not adequately visualized with IADSA alone, as single projections do not provide a sense of volume, and it may fail to detect an aneurysm if the lesion overlaps with nearby vessels. These concerns can be addressed by using 3D rotational angiography, which images the cerebral vasculature on many views. However, IADSA is costly and invasive with a 2-4% transient complication rate and about 0.5% of patients undergoing catheterization are left with permanent neurological complications (15, 16, 17). Typical complications include amaurosis fugax, hemiparesis,

confusion, muscle spasm, and aphasia. Because of these considerations and the knowledge that CTA and MRA are also effective tests, there is some debate over the best way to diagnose an aneurysm (18, 19, 20). Transcranial Doppler sonography has also been proposed as a method to evaluate the presence of aneurysms (21). See Table 2 for the sensitivity and specificity described for the various techniques. However, it should be noted that these numbers are based on studies with small sample sizes, and other methodological flaws, and at this time, the available data do not suggest that one modality is clearly superior to the others (3). It is also necessary to mention that the values found in Table 2 are highly dependent on the size of the aneurysm. If the aneurysm is <3mm, the sensitivity of MRA plummets to 38%, and the sensitivity of CTA drops to 61% (2). Because the technology in radiological imaging is improving rapidly with increases in resolution of all modalities, it is expected that the values listed in Table 2 will improve in the coming years. Illustrating this point, a recent study demonstrated CTA and IADSA to both have a sensitivity of 97% and a specificity of 100% when evaluating middle cerebral artery aneurysms. In 76% of the cases CTA was able to provide information not available on IADSA, suggesting that CTA, in its current state, may be superior to the "gold-standard" (22).

NATURAL HISTORY OF UNRUPTURED INTRACRNIAL ANEURYSMS

There is a great deal of controversy surrounding the natural history of unruptured aneurysms. It is such a hot-topic because knowing the likely course of aneurysms will play a pivotal role in determining the appropriate management. Unlike the more predictable course of abdominal aortic aneurysms, where the lesion grows in size and rarely ruptures before it reaches the threshold diameter of 5.0 cm, the data for intracranial aneurysms are much less clear.

Prior to 1998, the data available estimated the rupture rate for aneurysms to be 1 to 2.5% per year. This value indicates that over many years, the risk of rupture is very significant, and therefore, surgical or endovascular treatment is appropriate in patients with incidental aneurysms (23). However, in 1998, data published from a study called the International Study of Unruptured Intracranial Aneurysms (ISUIA) challenged many of the beliefs about the natural history of aneurysms. This study had both retrospective and prospective parts. The retrospective part found that in patients whose aneurysm measured <10mm and without a prior history of SAH, the risk of rupture was 0.05% per year and the risk of rupture for aneurysms >10mm was 1% per year (24). These data indicate that the rupture risk of aneurysms may be much lower than what was previously believed. This changes the recommendation for intervention, because if the data from the ISUIA are correct, the risk of intervention outweighs the risk of rupture in small aneurysms. The data from this study also indicate that the size of the aneurysm is the best predictor of future rupture, with 10mm appearing to be an appropriate cut-off point between small and large aneurysms. The location of the lesion also had an independent effect on the risk of rupture, with aneurysms in the posterior circulation having a higher risk (24). In 2003, data from the prospective segment of the study were published, and indicated the five-year rupture risk is 0% and 2.5% for small aneurysms in the anterior and posterior circulation, respectively. This portion of the study also suggested that the upper limit demarcation of a small aneurysm (thus, low of rupture) is 7mm, not 10mm as suggested by the retrospective segment of the ISUIA (25).

There are many criticisms of the ISUIA; a few of which are subsequently discussed. First, the patients with unstable aneurysms were selected out of the retrospective part of the study because they would have been treated upon the discovery of the lesion, and not included in the data. Second, cavernous carotid aneurysms were included in the study group, but these lesions generally do not produce SAH. Third, the annual incidence of SAH in the United States is about 30,000, which can be calculated to a rupture rate of at least 1% per year (23). These points suggest that the rupture rate suggested in the ISUIA may be artificially low.

Despite these criticisms, this was indeed a landmark study, and the clinical guidelines are based largely on the data from this trial. The current recommendations are observation, rather than intervention, in patients with incidental aneurysms <10mm. Exceptions include patients with growing lesions and those approaching 10mm, lesions with irregular morphological and hemodynamic features, and patients with multiple first or second degree relatives with a history of aneurismal SAH.

MANAGEMENT

The appropriate management for unruptured intracranial aneurysms does not have a clear evidence-based strategy. The risks of rupture must be weighed against the risks associated with intervention. Three main treatment options are available to the patient: observation, endovascular therapy, and surgical therapy.

In light of the ISUIA data, observation is a viable option in many cases. If this management is selected, it is important for the treating physician to be aware that aneurysms may grow unpredictably, so it is necessary to

serially monitor the aneurysm and watch for new-onset symptoms related to the aneurysm. Serial monitoring can be accomplished non-invasively with MRA, CTA, or possibly transcranial Doppler ultrasonography (see section on diagnosis). The parameters suggesting that a patient should not undergo intervention include: lack of symptoms, aneurysm size <7mm, lesion in the anterior circulation, age older than 64 years, and no personal or family history of SAH. Similarly, patients younger than 50 years with symptomatic aneurysms >25mm located in the posterior circulation and a personal or family history of SAH should undergo intervention (4). Of course, most cases fall somewhere in between these two extremes and the appropriate management is not obvious.

Approved by the FDA in 1991, endovascular treatment consists of guiding a catheter from the femoral artery to the cerebral vasculature via the ICA or vertebral artery, depending on the location of the aneurysm. The procedure is guided by fluoroscopy, and when the catheter has reached the aneurysm, several soft platinum coils are deployed in the lumen of the lesion. These coils completely fill the lumen and induce the formation of a thrombus to occlude the aneurysm, preventing future rupture (4). A wide neck and large size of the aneurysm make the procedure more difficult with poorer results. This procedure appears to be safe relative to surgical treatment, and it is able to treat lesions that are difficult to approach surgically, but there are questions regarding the durability of the endovascular technique. In most studies, complete occlusion is achieved in 80% to 90% of patients. At post-treatment follow-up, however, small neck remnants are common, and some degree of thrombus recanalization is observed in 50% of all patients and up to 90% of patients with giant aneurysms. Both neck remnants and recanalization are associated with a risk of rupture, and 20% of patients may require more than one coiling procedure (23). Contrast enhanced transcranial Doppler sonography has been shown by a small study to be sensitive and specific (100% and 97%, respectively) in the detection of clinically relevant residual flow in the follow-up of coil-embolized aneurysms (26). IADSA is effective in visualizing treatment failures with residual necks or complete recanalization, but 3D MR appears to be more effective in evaluating "partial treatments" (27), such as incomplete recanalization, which may prove to be useful in detecting treatment failures before they have the potential to hemorrhage.

Surgical clipping has been used for the treatment of intracranial aneurysms for longer than 40 years. This procedure involves placing a surgical clip at the junction of the healthy artery and the neck of the aneurysm. This treatment is very effective, demonstrated by annual risks of rupture following clipping reported from 0% to 0.9% (4,28). The disadvantage is the invasive nature of the procedure, which is associated with a higher risk of complications, and as with any surgery, elderly patients are less able to tolerate the trauma of the procedure. See Table 3 for a comparison of the two treatment interventions.

SUMMARY

Intracranial aneurysms are relatively common,

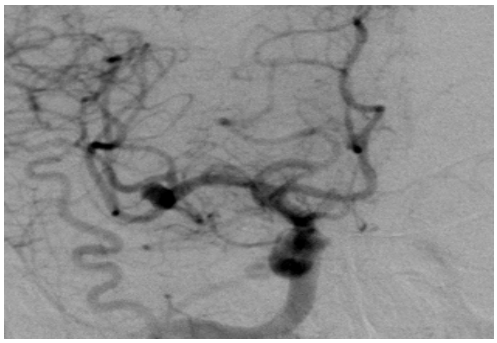

Figure 2. Bilobed aneurysm of the right middle cerebral artery measuring 4x5mm.

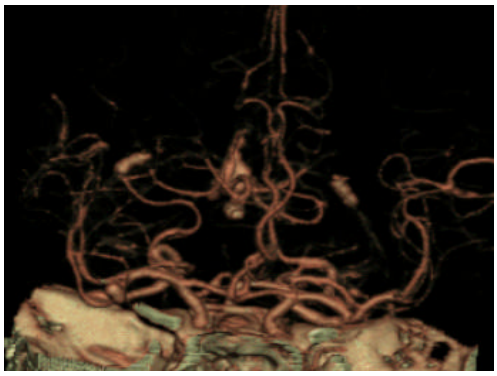

Figure 3. Computed tomography (CT) angiography of the same aneurysm depicted in Figure 2.

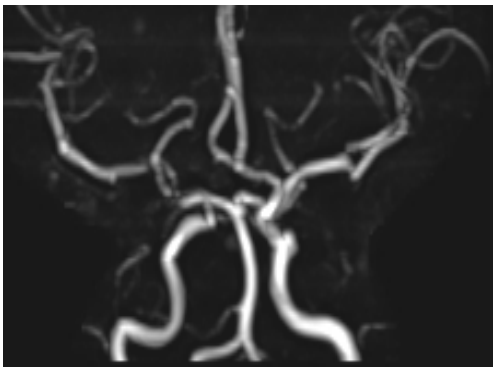

Figure 4. Magnetic resonance (MR) angiogram depicting normal cerebral vasculature

occurring in approximately 4% of the population. Most of these aneurysms are asymptomatic, and they carry a small but real risk of rupture, resulting in a subarachnoid hemorrhage. IADSA is the gold-standard for diagnosis of intracranial aneurysms, but CTA, MRA, and transcranial Doppler sonography are also effective diagnostic tests. These non-invasive imaging modalities are more appropriate for serially monitoring aneurysms because of the risks associated with invasive angiography. The natural history of intracranial aneurysms is still being explored, but our current understanding suggests that the annual risk of rupture is 1% or less. Large, irregularly shaped lesions arising from the posterior circulation are at an increased risk for rupture. The management strategies consist of observation, intravascular coiling, and surgical clipping.

REFERENCES

1. Rinkel GJ, Djibuti M, Algra A, et al. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998; 29: 251-6.
2. Gasparotti R, Liserre R. Intracranial aneurysms. Eur Radiol 2005; 15: 441-7.
3. Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. Brain 2000; 123: 205-21.
4. Wagner M, Stenger K. Unruptured intracranial aneurysms: using evidence and outcomes to guide patient teaching. Crit Care Nurs Q 2005; 28: 341-54.
5. Austin G, Fisher S, Dickson D, et al. The significance of the extracellular matrix in intracranial aneurysms. Ann Clin Lab Sci 1993; 23: 97-105.
6. Stehbens WE, Delahunt B, Hilless AD. Early berry aneurysm formation in Marfan's syndrome. Surg Neurol 1989; 31: 200-2.
7. Liebenberg WA, Worth R, Firth GB, et al. Aneurysmal subarachnoid haemorrhage: guidance in making the correct diagnosis Postgrad Med J 2005; 81: 470-3.
8. Gorelick PB, Hier DB, Caplan LR, et al. Headache in acute cerebrovascular disease. Neurology 1986; 36: 1445-50.
9. Friedman JA, Piepgras DG, Pichelmann MA, et al. Small cerebral aneurysms presenting with symptoms other than rupture. Neurology 2001; 57: 1212-6.
10. Wiebers DO, Whisnant JP, Huston J 3rd, et al. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003; 362: 103-10.
11. Rowley HA. Cerebrovascular Disease. In: Brant W, Helms C. Fundamentals of Diagnostic Radiology. Baltimore, MD: Williams & Wilkins; 1994.
12. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia 2003; 23: 935-41.
13. Novelline R. The Central Nervous System. In: Novelline R. Squire's Fundamentals of Radiology, 5th ed. Cambridge, MA: Harvard University Press; 1997.
14. Jager R, Saunders D, Murray A. Cranial and intracranial pathology (2): cerebrovascular disease and nontraumatic intracranial hemorrhage. In: Grainger R, Allison D, Adam A, Dixon A. Diagnostic Radiology: A Textbook of Medical Imaging, 4th ed. London, England: Harcourt Publishers Limited; 2001.
15. Leffers AM, Wagner A. Neurologic complications of cerebral angiography. A retrospective study of complication rate and patient risk factors. Acta Radiol 2000; 41: 204-10.
16. Waugh JR, Sacharias N. Arteriographic complications in the DSA era. Radiology 1992; 182: 243-6.
17. Warnock NG, Gandhi MR, Bergvall U, Powell T. Complications of intraarterial digital subtraction angiography in patients investigated for cerebral vascular disease. Br J Radiol 1993; 66 (790): 855-8.
18. Tipper G, U-King-Im JM, Price SJ, et al. Detection and evaluation of intracranial aneurysms with 16-row multislice CT angiography. Clin Radiol 2005; 60: 565-72.
19. Kouskouras C, Charitanti A, Giavroglou C, et al. Intracranial aneurysms: evaluation using CTA and MRA. Correlation with DSA and intraoperative findings. Neuroradiology 2004; 46: 842-50.
20. Chappell ET, Moure FC, Good MC. Comparison of computed tomographic angiography with digital subtraction angiography in the diagnosis of cerebral aneurysms: a meta-analysis. Neurosurgery 2003; 52: 624-3.
21. Turner CL, Kirkpatrick PJ. Detection of intracranial aneurysms with unenhanced and echo contrast enhanced transcranial power Doppler. J Neurol Neurosurg Psychiatry 2000; 68: 489-95.
22. Villablanca JP, Hooshi P, Martin N, et al. Three-dimensional helical computerized tomography angiography in the diagnosis, characterization, and management of middle cerebral artery aneurysms: comparison with conventional angiography and intraoperative findings. J Neurosurg 2002; 97: 1322-32.
23. Tummala RP, Baskaya MK, Heros RC. Contemporary management of incidental intracranial aneurysms. Neurosurg Focus 2005; 18: 9:1-7.
24. The International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured Intracranial Aneurysms-risk of rupture and risk of surgical intervention. N Engl J Med 1998; 339: 1725-33.
25. Turner CL, Higgins JN, Kirkpatrick PJ. Assessment of transcranial color-coded duplex sonography for the surveillance of intracranial aneurysms treated with Guglielmi detachable coils. Neurosurgery 2003; 53: 866-71.
26. Costalat V, Lebars E, Sarry L, et al. In vitro evaluation of 2D-digital subtraction angiography versus 3D-time-of-flight in assessment of intracranial cerebral aneurysm filling after endovascular therapy. Am J Neuroradiol 2006; 27: 177-84.
27. Molyneux A, Kerr R, Stratton I, et al; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002; 360: 1267-74.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

The medico-legal expertise: Solid medicine, sufficient legal and a measure of common sense

James D. Sullivan*

All through medical school, aspiring medical practitioners spend most of their time learning about the inner workings of the human body and study to pass their exams so that one day they may be in the position to accomplish that ever-daunting task, already pursued by their predecessors , to serve mankind, to restore normal health, to stamp out disease, to prevent its occurrence, explain sicknesses to patients and stay out of jail. Once in practice however, the physician may be called upon one day to assess medico-legal aspects of a case in his practice or that of a colleague, something he may never have been shown how to do while in medical school.

Has the point of Maximal Medical Improvement been reached, is there an impairment? A functional limitation? A temporary or permanent disability? A handicap? Did the incident cause the injury and the sequelae? Is there an apportionment? An aggravation of a pre-existing condition? Is there evidence of malpractice? Is the individual employable? Part-time or full-time? Are there other investigations or treatments to come? Would you be willing to testify in court?

Answers to these questions are equally important in the overall helping of mankind, particularly for the great multitude toiling in the manual working class who are most often subjects involved in the medico-legal process. Because such people seldom have the capabilities of changing careers in mid-stream, they require some form of support should they become unable through misadventure to continue in their chosen pre-injury line of work.

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THE EXPERT

The physician who feels drawn to get involved in medico-legal matters is usually a specialist in practice for at least 10 years (orthopaedics and psychiatry are the most common) and begins to take on cases (expertises) from publicly-funded agencies such as the Workmen's Compensation Board, Provincial Automobile Insurance, Pensions Board, the Military. In time, depending on his performance and reputation, other agencies may come calling: Insurance Companies, individual legal firms, medical protective agencies, unions. Although the various mandators want the same answers, each one words their questions differently to suit their ends and each produces different guides for the evaluation of permanent disability. The old adage of "caveat emptor" for the employee, perhaps thinly veiled, can still be seen to be present.

The physician who does "expertises" becomes known as an "expert" not so much because he holds every discernable award or has performed brilliantly on the medical stage in his speciality, but rather because he has the required training and experience and is expected to know everything there is to know about the medical side of things in the case at hand, is expected to be available, willing and able to explain the issues on paper and, if required, as a witness in court. While in court, he must also be prepared to debate certain controversial issues arising from the case while addressing members of the legal profession and defend his opinion if such is contradicted by equivalent "experts" for the opposition. At all times, he must remain focused and informative and refrain from allowing personal feelings from intruding into his deliberations. He is there at the behest of the court and must remember to address his words to the judge who ultimately will make the final decision. His main purpose is not necessarily to beat down the

opposition but to adequately represent the medical interests of his client.

THE PHYSICIAN WHO FEELS DRAWN TO GET INVOLVED IN MEDICO-LEGAL MATTERS IS USUALLY A SPECIALIST IN PRACTICE FOR AT LEAST 10 YEARS…

To become an efficient expert, the physician can gain knowledge of the process by following degree-bearing university courses, attending refresher courses, reading journals and books on the subject or belonging to societies of like-minded practitioners, while all the while learning the language of the court and finding out what is expected of an "expert" in medical matters.

Before entering into an agreement to act as an expert witness, the physician must assure himself and his mandatary (requester of a mandate) that there exists no conflict of interest between himself and the case at hand. Otherwise, he should disqualify himself. The mandate (the actual request, specified questions asked and expected to be fully answered and reasons given for the answers) should be clearly enunciated in writing, authorised by the client, accompanied by all required medical documents concerning the case. Discussion of fees for the expertise, the cost of going to court, should be discussed and agreed to before proceeding. The claimant must be made aware that the physician chosen for an expertise is acting as an evaluator, and not as a treating physician. An expert gains more credibility when he chooses to diversify his allegiance as evaluator between plaintiff and defendant. Some experts occasionally referred to as "hired-guns" who remain on call solely to one or the other party, refusing to deal with either side of the picture, have an unsavoury reputation in the field of medico-legal expertise. Their views may be stilted preventing an unbiased appraisal of the facts.

THE REPORT

THE PHYSICIAN MUST ASSURE HIMSELF AND HIS MANDATORY THAT THERE IS NO CONFLICT OF INTEREST BETWEEN HIMSELF AND THE CASE AT HAND.

For the expert to have respect for the claimant goes without saying. No matter the circumstances of the claim, the expert listens to the story that is given and attempts to know as much of the details as is possible, somewhat in the manner of a detective , uncovering the truth in a methodical way. He records and lists all documentation received either from the mandatary or the client. He must try to keep the story in line and proceed chronologically through the events. He uses simple clear, language and takes great pains to ensure that he will not be misunderstood. His impartiality and transparency must be displayed at all times. Past and present history is important especially if the claimant already has suffered an injury at the same site. Habits such as smoking and taking medication should be recorded as well as past and present surgeries and hospitalisations.

Physical examination must be thorough and painstaking, known objective tests mentioned, measurements recorded, manoeuvres performed and fully described to verify the presence of a physical ailment in cases where "illness behaviour" is suspected. If such is difficult or impossible to ascertain (the client refusing to cooperate), the expert must explain why in his report, while never straying from the preset confines of his own speciality. In orthopaedics, when a certain part of the body is clearly the part to be studied (a broken ankle), all pertinent tests are required to be done so that as much information as possible is available for review. In dealing with the appendicular skeleton, as opposed to the axial skeleton, comparison with the opposite normal side is usually useful. A problem at times arises when the condition straddles the border between the axial and the appendicular skeleton (pain in the neck and the arm, pain in the back and the leg). In such cases, there may be more than one pathology to explain the symptomatology and signs. Similarly, for pain and dysfunction in an arm or leg, all parts must be carefully examined to include all probable pathologies, some being dominant, others subordinate. In rare situations, the "expert" is asked to determine if injury to one part of the body may have contributed to signs and symptoms arising in another part (shortened leg causing problems in the opposite leg or in the back). Injuries to parts of the skeleton carry sequelae that may take a while to show up (avascular necrosis of the head of the femur after a hip fracture). Referral to specific research data as found in the literature may be helpful to the expert, while dictating his summation, in explaining the general principles involved and how they may or not pertain to the case at hand. Recent publications are preferred and references always given.

The court will usually be satisfied with simple answers that get quickly to the point. Elongated, tortuous arguments will be difficult for non-medical participants to follow and can more likely serve to open the door to conflicting and burdensome counterinterogation. The "expert" speaks to the court and not to colleagues at a medical meeting.

As to the correct medical diagnosis, the expert is expected to be clear and concise and if required, because of the debatable nature of a condition, give all

the appropriate reasons for his choice. He must state the reasons as to why he feels that a certain diagnosis exists and another does not. In some cases of course, a clear and concise diagnosis may not be possible. The expert must then rely on the "balance of probabilities" in producing the best diagnosis possible and elaborate on his reasoning. In deciding whether the claimant has reached a point beyond which no further investigation or treatment is indicated, known as the consolidation point or point of maximal improvement, a study of the evolution of the condition and the response to treatment is carried out. If no further improvement is noted during the post-op visits, if the physio reports indicate an unchangeable level of return of function, strength, range of motion, and pain, if repeated xrays and other tests are unchanged, the expert, by all rights, declares that the condition is now medically stabilised and nothing further can or need be done.

THE REASON WHY THINGS HAVE PROGRESSED TO A LEGAL DEBATE IS BECAUSE THE ISSUES ARE CONTENTIOUS (MORE GREY THAN BLACK OR WHITE).

In explaining possible cause and effect relationships, the expert is guided by the nature and intensity of the trauma, the elapsed time between event and the complaint, related events both prior and following, the coherence of impact-anatomical site-and type of injury sustained, the quantity and quality of the symtomatology, the pre-morbid state of claimant, the natural history of the condition, and all other associated diagnoses and treatments. He includes medical opinions by specialists solicited by the treating physician during the course of medical treatment. He reports results of the laboratory tests and xrays. He wraps things up with a summary and conclusions and then goes on to answer the questions asked by the mandator. He does not venture into areas that are not solicited although he should make a mental note of these and be prepared, should the opposition wish to bring them up, to face those issues with compelling arguments.

He gives reasons for his answers which he knows he can uphold in a court of law. In citing from the medical literature, it is always safer to quote articles dealing with basic principles already agreed upon and the natural course of the condition including known complications rather than with gratuitously expressed personal assertions and opinions which can easily be countered by the opposition. It is important to give a reference when citing a percentage disability. Published guidelines are usually available. There are rare instances where the actual medical diagnosis defies categorization (pain syndrome, partial nerve injury). In such cases, the expert may need to revert to analysis by analogy to a similar condition occurring in a different body system.

At other times, an expert is asked to produce a counter-expertise to one already submitted by the opposition. Such cases may be more demanding on the part of the expert and require more experience. The process to follow however is the same although more specific on certain points of contention.

THE LEGAL SIDE

The purpose of being engaged in a medico-legal dispute is to be able to convince the judge that you have a better argument than the opposition, in short, to win the argument based on the presentation of more credible evidence. The reason why things have progressed to a legal debate is because the issues are contentious (grey rather than black or white).

Although the main duty of the physician is to clearly explain the medical side of things, that of the lawyer is to argue and win the argument on points for his client. The lawyer relies on the physician to provide him with the necessary medical information which he will weave into legal dissertation which he hopes will convince the adjudicating body of the correctness of his proof on behalf of his client. The idea is that neither the physician nor the lawyer should see themselves as individuals but rather as members of a team of fact finders and expositors, working in tandem, bringing to light the true nature of the dispute, enabling the judge to be well informed, weigh the arguments, see the truth, and find for their side. Hard honest work and common sense will usually provide the necessary tools for the construction of a winning case. Teamwork is essential, neither doctor nor lawyer ever trying to outdo each other. Winning for the client is key. The preset rules of the legal system already established and improved over the years will, when well fed and properly oiled, provide the energy to see the case through and allow for an orderly and compelling presentation of the facts. However good the arguments are, the ultimate decision will always reside with the judge or jury. If a side feels it has been denied justice, there is always the appeal process to fall back upon.

In his report, the physician must clearly state and distinguish what is said by the claimant, by the consultant, by the therapist, by the nurse and under what circumstances. He must keep the narrative in order and record the train of events in a consecutive manner. If there are long unexplained gaps where very little happened medically - "un silence medical" -he must explain the reason. He must refrain from giving a personal opinion as he discusses the facts, even though

he may not be in agreement with the medical decisions taken in the case. A factual, objective and non-judgemental exposé of the case is always called for. The physician will find this tack much easier to defend when called upon to explain his written report orally in court. When interrogated by counsel for the opposition, the medical expert can expect to be protected by his counsel should the questioning become off-base. There is no need to become argumentative with opposing counsel.

THE PHYSICIAN'S REPORT MUST BE SUFFICIENTLY FACTUAL AND APPROPRIATELY WORDED TO DISPEL ANY THOUGHTS AS TO THE HIGH STANDARD OF HIS PROFESSIONALISM AND CREDIBILITY

The physician must remember that a great probability exists that a host of others will most likely read his report and make comment and that no one is ever neutral in debate. His report must be sufficiently factual and appropriately worded to dispel any thoughts as to the high standard of his professionalism and credibility.

To determine whether an aggravation of a previous condition at the same site has occurred is not an easy task and may become a much debated point. One point of view that has merit in my view is that if the previous condition was entirely dormant and only reappeared as a result of the sustained injury (e.g. latent osteomyelitis reappearing after an injury to the same site), then grounds for an aggravation can be entertained. On the other hand, if the previous condition had already been noticed to be causing symptoms and signs by the patient or his treating physician, then a second injury at the same site would not be seen as being responsible for the aggravation.

The same is true for the establishing of functional limitations following an injury which has left a degree of permanent injury. There is no tried and tested way of doing this and one relies on a number of factors, not the least of which is a good measure of common sense. First of all, we all know of individuals who are handicapped but in no way disabled for doing the same work they did before the injury. The body and the mind have a great way of compensating in the willing subject. The employer as a rule wants to hire able bodied individuals capable of doing the tasks that go with the job. You can either do it or you can't. If Mother Teresa was the boss of a private enterprise, she would probably act the same way. If the individual clearly cannot do the job (the job requires two good legs and he only has one), then clearly professional reorientation is called for. But if the claimant has two good legs, but one is shorter than the other by 0.5 inches, normally this would not present a functional deficit. Again, if the claimant has two good legs and one hurts but has good strength and a normal range of motion, this would also not normally constitute a functional impairment. While taking into account the claimant's sequelae after injury and the listed demands of the targeted job, the expert usually allocates as few functional limitations as possible in keeping with the described disability, only those that will impact directly on his pre-injury job. Too many limitations would disqualify the claimant from returning to work either with the same employer or a competitor.

A good and trusted worker will also find it easier to return to work. A worker with a bad reputation will likely not be so fortunate. Goodwill must exist on all sides. In syndicated workers, the union representative will often wish to be part of the medico-legal proceedings. At times they have tried to influence medical decisions and be present at the actual medical examination of the worker. It is my belief that there is no rule that says they should be present and the expert, while accepting the fact that the union is there to protect the workers' rights, has every right to deny the union's presence in the examining room. The union however has the right to contest the report if it feels their justice standards have been denied. In general, a third party is inadmissible during a medico-legal examination unless that party is present as a designated expert (translator, deaf-mute sign specialist).

THE ASSESSMENT OF PAIN ON ITS OWN MERITS, IN THER FACE OF NORMAL SENSORY AND MOTOR FINDINGS OF A PART, REQUIRES A FAIR BIT OF KNOWLEDGE AND EXPERIENCE.

The assessment of pain on its own merits, in the face of normal sensory and motor function of a part, requires a fair bit of knowledge and experience. A great number of contested cases hinge around this very subject. Some pains are tolerable by the claimant and are covered by the disability process and the resulting functional limitations. Some pains are all encompassing and of themselves prevent the worker from carrying out the regular activities of daily life, let alone work-related tasks. Published criteria (AMA Guidelines to the Assessment of Functional Disabilities, 2001) exist for the establishing of disability in such cases. It remains for the expert however to adequately categorize those pains which the claimant alleges keep him from performing his regular pre-injury job despite the lack of objective evidence of motor or sensory dysfunction. In some mandates, without objective clinical (not merely

radiological) evidence, the expert cannot establish a defensible percentage disability. In other mandates however (Société d'Assurance Automobile du Québec) there is allowance for the inclusion of certain pain modalities as such in the granting of disability (préjudice non-pecuniaire). This area, so often debated and still shadowy, clearly requires further defining and will need time to do so.

The world of the medico-legal expertise can be both medically beneficial to the claimant and a compelling and interesting medical exercise for the expert. A well done expertise containing accurate medical information and providing objective and clear answers to the questions asked will usually determine the correct path for an injured worker to follow post injury and by so doing, can serve as a liberating and even a therapeutic force. The art and science of medicine combine to shed light in the arena of social justice.

As to aspiring physicians still in medical school, although their curriculum is already overcharged, some of the aspects of this type of medicine included in their curriculum would, in my opinion, teach them the reach and application medical science can have in the lives of a sizable group of workers at large, beyond the more protected confines of the hospital, the library, the operating room and the office.

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CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Scrutinized: The TRIPS Agreement and Public Health

Junaid Subhan*

SUMMARY

The World Trade Organization's (WTO's) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of 1994 seeks to implement a uniform set of intellectual property protection across member nations to provide greater stability in international economic relations. Critics argue that the TRIPS agreement provides unnecessarily strong protection of intellectual property rights which serves to prevent the ill in developing nations from having access to affordable essential medications.

The first recommendation that this paper makes is to provide two sets of intellectual property protection, one that applies to essential medications such as AIDS drugs and certain antibiotics and another that applies to drugs that treat non-life threatening conditions.

The second recommendation builds upon the first recommendation: if two sets of intellectual property protection legislation are enacted, patents on essential medications should be restricted to patents on processes rather than the product itself.

The third recommendation seeks to amend the language of the TRIPS agreement to make it obligatory for member nations to implement provisions on compulsory licensing within their domestic legislation.

INTRODUCTION

At the junction of the medical sciences, public health, economics, political science, business and law lies a fascinating crisis facing much of the developing areas of the world. The question of providing access to essential medications for the third world is a complex one and faces many barriers to a solution. Diseases like AIDS, malaria, and tuberculosis have been ravaging the developing world for decades; despite the efforts of NGO's, governments, health professionals, lawyers and even major pharmaceutical companies, a solution to these problems is nowhere in sight.

Socio-political factors play an important role in the rampant spread of disease in underdeveloped nations. The scarcity of basic infrastructure in developing nations, such as roads and transportation for access to hospitals, the neglect of the typically substantial rural population and basic sanitation to prevent the spread of disease, are all concerns that must be addressed to quell the public health crises facing these countries. Government instability, corruption and inefficiency are factors that exacerbate the situation (1).

Scientific and medical problems are an added burden on developing nations. Cures for some of the most devastating diseases such as AIDS and malaria are unavailable. Prevention strategies are falling on deaf ears due to time-honored views and social stigma. With a few exceptions, inadequate education of the public serves to perpetuate these counter-productive notions. The lack of health care professionals to administer sophisticated drug regimens and ensure proper compliance with prescriptions is a further challenge (2). The commercial side of this issue cannot be ignored. Pharmaceutical companies are just that, they are commercial entities and as such have a profit motive.

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Although the ethics of their position can be endlessly argued, they view their primary responsibility to be towards their shareholders and investors. Consequently, the pharmaceutical industry has concentrated their research and development efforts in areas that are likely to be profitable, such as drugs for conditions prevalent in developed regions. Malaria, schistosomiasis and other such conditions do not present the potential for lucrative returns and so are often neglected in commercial research.

Of all the challenges facing developing nations with respect to public health, none has garnered nearly as much attention as the legal facet of the problem. It has been repeatedly argued on one side that stringent intellectual property legislation keeps drug prices too high and as a result makes them less accessible to those who need them the most (3). The other side contends that intellectual property laws are required to foster innovation and create reward incentives for pharmaceutical companies to invest in risky research and development (4). This paper will examine the underpinnings of globalized intellectual property law and its effect on developing nations and make three recommendations that seek to better implement public health concerns into the existing legal framework.

BACKGROUND

WTO

The World Trade Organization is the body that regulates international trade amongst its member nations. It is the only such organization in the world and thus has tremendous influence over international trade policy. While bilateral and multilateral free trade agreements exist and are permitted under the provisions of the WTO, no other agreement has been as much of a driving force behind the globalization and liberalization of trade barriers as the set of agreements that comprise the WTO. The WTO allows representatives of member countries to come together to form the agreements that are central to the functioning of the WTO and the expansion of global trade. There are three such agreements: GATT (the General Agreement on Tariffs and Trade), GATS (the General Agreement on Trade in Services) and the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement (5).

TRIPS

The TRIPS agreement has played a central role in the debate on providing access to essential medications to countries of the developing world. TRIPS is a WTO agreement that was negotiated in the Uruguay Round of negotiations from 1986 to 1994 by the members of the WTO (80% of the world's nations and the vast majority of the world's trading nations) that sets out certain rules regarding intellectual property rights (5). Once the member countries agree to the provisions, it becomes an official agreement of the WTO that must be ratified by member country governments in their own parliaments. The effect of this is to create a world standard of intellectual property protection. Agreements ratified by the WTO set out certain minimum standards; member countries reserve the right to go above and beyond the provisions of the agreements as long as domestic legislation does not controvert the conditions set out by the WTO agreements.

The purpose of the TRIPS agreement is to establish a uniform set of rules across the globe that would provide adequate standards of protection for intellectual property and provide greater predictability and stability in international economic relations (5). At this point it is important to note that the TRIPS agreement applies to all forms of intellectual property: from copyrights to trade secrets, however, this paper will focus on the TRIPS agreement as it relates to patent protection; and its impact on the accessibility of medications. The regulation of intellectual property rights has not always been of primary importance in the international arena. In the latter half of the twentieth century, the proliferation of high-technology devices, and the means to reproduce them at low relative cost, has made it essential to preserve an environment that encourages innovation. Industries that invested heavily in research and development, such as the information technology industry, were seeing their work pirated by other companies and sold for a fraction of the price offered by the inventors. This created an environment that was more profitable to "second-movers" as opposed to first-movers[1] and thus heavily discouraged innovation. Before the enactment of the TRIPS agreement, international intellectual property rights were governed by the Paris Convention on the Protection of Industrial Property which was first drafted in 1883. It was widely recognized in economic and commercial circles that the Paris Convention was inadequate to address modern issues of concern in industries such as information technology and biotechnology: there were few rules dealing with patents, no minimum period of patent protection, and no mention of the exclusive rights of patent-holders. The TRIPS agreement was the modern-day solution to this problem; it took, as its foundation, the provisions of the Paris Convention and the majority of the provisions of the Berne Convention for the Protection of Literary and Artistic Works. To this foundation, the TRIPS agreement added several other

[1] "First-movers advantage" is a fundamental commercial principle that states that the first company to fill a market segment enjoys a significant competitive advantage over future competition

specifications that addressed the inadequacies outlined above (5). Any nation that wanted to take part in the World Trade Organization was obliged to amend its intellectual property legislation to meet the guidelines set out in the agreement, thus creating a uniform international standard of protection for intellectual property rights.

The provisions of the TRIPS agreement range from the mundane to the controversial. Included in its terms is a minimum period of patent protection of twenty years from the date of filing for a patent. Significantly, the TRIPS agreement also invalidates the use of process patents by declaring that patent protection on a process extends to the product of that process. In addition to these provisions, the TRIPS agreement sets out two mechanisms that deal with international public health crises: compulsory licensing and parallel imports (5).

Compulsory licensing

Under article 31 of the TRIPS agreement (6), the rights of patent holders can be circumvented in certain situations. More specifically, member governments are given the authority to grant a license to a party willing to commercialize an invention protected under patent without the consent of the patent holder. Unless there is a "national emergency", the proposed licensee is required to make reasonable efforts to seek a voluntary license (6). If the patent holder refuses to grant a license, a non-exclusive license can be granted by the government. Consequently, subject to other provisions of the TRIPS Agreement, compulsory licensing allows generic drug companies to manufacture patented drugs and sell them at a fraction of the price that the patent holders would, since only the costs of producing the medication and not the costs of research and development need to be recovered. Critics of the compulsory licensing provisions point to paragraph (f) under the same article which specifies that compulsory licensing must be used "predominantly for the supply of the domestic market of the Member authorizing such use" (6). These critics contend that this clause makes it exceedingly difficult for governments of developing nations to issue compulsory licenses to quell public health crises because it would require that the drugs be manufactured in developing countries where little infrastructure exists to support this ultra-sophisticated industry (7).

Parallel importing

Parallel imports allow a developing nation to take advantage of the common practice of differential pricing of drugs across different countries. For instance, if a package of Nevirapine, a patented drug, is being sold at $250.00 in France and at $275.00 in South Africa, a South African company (or the government itself) can import the drug from France and sell it at a lower price without the authorization of the South African patent holder. Parallel imports effectively allow countries to purchase patented medications at the lowest global price. The right to parallel import under the TRIPS agreement is based on a fundamental legal principle called "exhaustion" of intellectual property rights which defines the point at which a patent holder ceases to have exclusive rights in the context of re-sale of its product (5). Article 6 of the agreement states that member countries can independently decide at which point the exclusive rights of patent holders with respect to re-sale are terminated, but issues of exhaustion cannot form the basis of a dispute brought to the WTO for resolution. In effect, article 6 of the TRIPS agreement allows member countries to engage in parallel importing.

Doha declaration on TRIPS and public health

Although these provisions were in the TRIPS agreement since its inception, nations never interpreted the provisions of the agreement in a manner consistent with the promotion of public health. Certain nations that were subject to the TRIPS agreement would enact legislation that maximized the protection of intellectual property rights but ignored public health crises affecting developing areas. Further and perhaps even more damaging, at the behest of the influential pharmaceutical lobby developed nations would threaten sanctions on countries that attempted to take advantage of parallel importing or compulsory licensing. For example in 1997, the United States notoriously threatened trade sanctions against South Africa unless they repealed a section of the Medicines and Related Substances Control Amendment Act which allowed compulsory licensing and parallel importing, despite it being TRIPS compliant (3, 8).

It was these events that drew the ire of public health advocates worldwide. At this point the WTO acknowledged the weaknesses inherent in their agreement and recognized that the TRIPS agreement must be interpreted and applied in a manner that took into consideration the health care crisis facing the developing world.

On November 14, 2001 in Doha, Qatar a historic declaration was made by the WTO. The member governments agreed on an independent declaration relating to the TRIPS agreement and its role in alleviating public health crises worldwide (9). There were three primary concerns about the TRIPS agreement that were addressed by the Doha Declaration (5). First, there were doubts as to whether the member nations would interpret the TRIPS agreement in a

manner that favoured the advancement of public health. To address these doubts, in paragraph 4 of the Declaration, the member nations asserted the Agreement's compatibility with public health and the right of member nations to interpret the agreement with the aim of improving public health crises.

Second, concern was expressed about the pressure being placed on developing nations to omit TRIPS measures that favour public health from their legislation. To allay this concern, it is reiterated in numerous instances throughout the Declaration that nations have the autonomy to enact their own legislation without influence from external actors. Although redundant declarations without concrete steps forward may seem inconsequential, it is customary in international law to first build consensus on certain principles and then eventually move nations to adopt policies consistent with those principles (10).

Third, and most importantly, the practicality of the provisions on parallel importing and compulsory licensing were questioned. In paragraph 5 (d), it was clarified that member nations have the right to engage in parallel importing, in particular, without interference from external actors. A further concern, as previously mentioned, was that compulsory licensing would only be allowed if it was used to supply the authorizing country's domestic market. This meant that developed nations could not authorize compulsory licenses for the supply of medications to developing countries. A compulsory license could only be used to supply a developing nation if the proposed licensed product was manufactured in its jurisdiction (11). The difficulty with this situation is that developing nations rarely have the infrastructure required to support a stable pharmaceutical industry. Paragraph 6 of the Declaration (9) addresses this:

> "We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002."

Doha assignment

Paragraph 6, called the Doha Assignment, was clearly the most progressive aspect of the Doha Declaration; it called for a revision of one of the TRIPS agreement's greatest obstacles to access to medication. Unfortunately, the WTO was unable to come to an agreement by the end of 2002 (5).

Criticism of the WTO mounted because of their perceived complacency in dealing with a change that would affect the lives of millions; but they finally came through on August 30, 2003 with a consensus on how to improve the compulsory licensing system (12). Under the agreement, all least developed countries[2] that are WTO members will be exempted from the requirement of themselves producing patented drugs under compulsory license. Furthermore, countries that fall outside the least developed country definition can issue a compulsory license (if the drug is patented in its jurisdiction) for the supply of a developing country if that country's public health situation falls under certain criteria:

- Evidence of a public health concern
- Evidence that the importer's pharmaceutical industry is non-existent or inadequate.
- Proof that the drug will be used only for public, non-commercial purposes.

It was further stated in paragraph 11 of the agreement that amendments to the TRIPS Agreement to reflect these decisions would be made by June of 2004; thus giving it full legal force at that time.[3]

In a press release, WTO Director-General Supachai Panitchpakdi called this decision a "historic agreement". Panitchpakdi further elaborated: "It proves once and for all that the [WTO] can handle humanitarian as well as trade concerns. This particular question has been especially difficult. The fact that WTO members have managed to find compromise on such a complex issue bears testimony to their goodwill." (5) Leaders across the developed world touted the decision as a spectacular development in international intellectual property law. Kofi Annan, the UN Secretary-General, stated that "intellectual property protection is key to bringing forward new medicines, vaccines and diagnostics urgently needed for the health of the world's poorest people. The United Nations fully supports the TRIPS agreement - including the safeguards incorporated within it." (13)

RECOMMENDATIONS

The TRIPS agreement is the sweet spot on the punching bag that is the World Trade Organization. Fairly or not, the TRIPS agreement is alleged to be a monstrosity of modern capitalism. Says Noam Chomsky, a renowned academic: "There is nothing

2 Least developed country (LDC) as defined by the UN. Of the 50 LDC's, 32 are WTO members.

3 The June deadline passed without any consensus, the deadline was then extended to March of 2005. The March deadline also passed without any agreement, however on the 6th of December 2005, the WTO finally came to a consensus on the amendment to be made to the TRIPS Agreement. This amendment follows the principles agreed to on the 30th of August 2003. Member nations have until the 1st of December 2007 to ratify the amendment so that it can be formally included into the TRIPS Agreement.

liberal about [the TRIPS agreement]. It is a highly protected system, designed to ensure that private tyrannies, which is what corporations are, monopolize the technology and the knowledge of the future." (14) Dr. Zafar Mirza, Executive Coordinator of The Network, a Pakistani health advocacy group, asks "They are talking about harmonizing trade policies, but nobody is saying a word about harmonizing the socio-economic conditions of the world. All countries are at different stages of development, how could they be governed by the same law?" (15) These comments stand in stark contrast to those quoted above by high-profile public officials. Why is one group so staunchly opposed to the TRIPS agreement, while another shows seemingly infallible support? The second part of this paper seeks to reconcile these two views.

Criticism of the TRIPS agreement arises on a number of levels. There are those who criticize the implementation of its provisions in sovereign countries, there others that criticize the provisions of the TRIPS agreement and there are still others who criticize its very existence. The subsequent critique of the TRIPS agreement will be made through the lens of the following neutral principles in order to make the recommendations as relevant and applicable to the current situation as possible:

- Access to essential medications is a fundamental human right.[4]
- Intellectual property legislation has been a driving force behind innovation for commercial purposes.[5]
- The world's primary source of novel and generic drugs has been and will continue to be the commercial pharmaceutical industry.[6]
- The TRIPS agreement will not be repealed in the near future and will continue to shape international intellectual property law.[7]

Access to essential medications is a fundamental human right and as such, it trumps all other claims in this issue. The reason this issue is so complex and so hotly debated is that in order to satisfy this right, the right must be conceded. In other words, in order to finance the development of essential medications, the producers of these medications must be financially compensated from the users of the medications who, in this case, cannot afford them. In theory, since access to essential medications is a fundamental human right, those who cannot afford these medications should have them provided at no cost or at a reasonable cost. From the above argument, the problem facing the TRIPS agreement in the context of global public health is defined: the fundamental human rights of those in the developing world must be respected without hindering the development of novel medications that serve to advance the satisfaction of this right.

The following recommendations keep the above arguments front and centre and attempt to improve the public health situation within the framework of the existing TRIPS agreement.

Recommendation 1: Define the term "essential medication" within TRIPS.

Patents can be applied to a wide variety of technologies; from the most complex and sophisticated piece of computer software to the most mundane hinge, nut or bolt. Even within the pharmaceutical industry, products under patent vary greatly. With this immense variance, should a patent on a drug for AIDS be treated in the same way as a patent on a drug for erectile dysfunction or high cholesterol?

A wide array of drugs are developed and manufactured by pharmaceutical companies and the TRIPS agreement must differentiate between patents for Viagra and patents for Efavirenz. It is reasonable to demand full 20-year intellectual property protection for "chemical toys" (17) but when it comes to life-saving essential medications certain concessions in favour of the promotion of public health must be made. The term "essential medication" should be defined under the TRIPS agreement, not in reference to a list of diseases, as has been proposed in the past (18), but rather as a general description of what constitutes the difference between an essential and a non-essential drug. Possible criteria for inclusion into such a category would be:

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[4] Article 25.1 of the Universal Declaration of Human Rights (16) states: Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control.
Article 28 of the Declaration further asserts:
Everyone is entitled to a social and international order in which the rights and freedoms set forth in this Declaration can be fully realized.

[5] This claim is more or less incontrovertible; executives of the pharmaceutical industry, officials of the UN and the WTO, NGO's lobbying against TRIPS and other detractors wholeheartedly agree on this principle according to all sources researched.

[6] The "commercial pharmaceutical industry" includes generic drug companies as well as research & development based drug companies. Though recently a few enterprises have been receiving publicity for their innovative approach to financing the research and development of neglected diseases, they are exceptional cases. Presently, the vast majority of the world's supply of drugs comes from the commercial pharmaceutical industry. This does not seem likely to change in the near future.

[7] This statement is irrefutable and redundant but will play an important role in the critique. Its function is to narrow the scope of the critique to the provisions and implementation of the TRIPS agreement itself and not its existence, nor factors outside of its jurisdiction. The idea is to make the recommendations directly applicable to the current legal framework.

availability of alternative treatment, severity of the disease the medication is aimed at treating, and the capacity of the patent-holder to adequately supply markets that demand the patented product. For separate definitions to be beneficial though, separate provisions should be made where appropriate. Ideally, two separate sets of patent legislation would exist in parallel; one applying to medications deemed essential and another applying to non-essential medications.

By creating separate categories of drugs, the TRIPS Agreement can more properly balance intellectual property protection of drugs with their purpose of healing as many of the ill as possible. Such a system can encourage innovation by increasing the potential rewards of a successful discovery of a non-essential medication. Simultaneously, access to essential medications by patients in developing areas can be improved by placing fewer protections on the intellectual property behind these medications.

There is, however, one glaring problem with this recommendation; creating a two-tiered system of intellectual property protection, where one set of drugs is given stronger protection than the other, will likely drive research investment into the more strongly protected class of drugs. The solution to this is surprisingly simple: because two classes of drugs are established, additional rewards that do not interfere with access can be implemented in the class of drugs that is less protected. For example, patents on essential medications could be restricted to process patents alone; in exchange, duration on a process patent could be extended beyond twenty years. Because two separate categories of drugs are defined, product patents would be maintained on all patentable goods other than essential medications, including non-essential drugs.

In effect, creating separate categories of intellectual property protection for disparate classes of drugs allows for customized protection that can both promote innovation and uphold the fundamental human rights of those in need of essential medications.

Recommendation 2: Allow process patents

Two types of patents exist: process patents and product patents. Process patents are those that apply to the method of making or manufacturing an invention. This stands in contrast to a product patent which is a patent on the good itself (the product of the process). Under a product patent, a particular invention is protected regardless of the method used to manufacture it, on the other hand, under a process patent only the particular method for making the product is protected. It then follows that a process patent affords its holder less protection on its intellectual property than a product patent.

To implement this recommendation, paragraph (b) of article 28.1 of the TRIPS agreement, which states the rights of process patent holders, would need to be amended. This paragraph states that the rights of a process patent holder extend to the product obtained from the process and are not restricted simply to the process itself, thus effectively eliminating the notion of process patents from the TRIPS agreement (6).

The most appealing aspect of process patents is that they are at the very core of what capitalism represents: competition, efficiency and profitability; yet applied in the correct way, they can be extremely beneficial to patients in the developing world. Most research-based pharmaceutical companies would likely disagree with this view and would argue that a process patent provides little incentive to invest in risky research because another company can simply reverse engineer a medication to find an alternative method of producing the product, thus bypassing the process patent. However, process patents in this situation can prove to be acceptable to research-based pharmaceutical companies and can improve the public health situation in developing areas.

Process patents provide a lower standard of intellectual property protection and thus encourage competition which in turn serves to decrease market prices. If a product is under a process patent, it encourages competing companies to invest in research to develop a method of producing the product in question more efficiently than the current standard. Unless the newly developed method is more efficient and cost-effective, the developing company would not be able to commercialize the product because the more efficient and cheaper product would be preferred by consumers (and third-world governments). Hence, a process patent inherently encourages the development of the most efficient and cost-effective method of producing the patented product, theoretically resulting in lower prices.

The drawback of process patents (and the likely reason they are barred from use under the TRIPS agreement) is that they only allow research-based pharmaceutical companies to maintain a patent monopoly until a second developer finds a more efficient way to produce the drug. This would typically shorten the period of patent monopoly that the discovering company is entitled to; however it provides other companies with an opportunity to earn increased profits by improving on the drug in question. In order to make the notion of process patents more amenable to research-based pharmaceutical companies (and thus more agreeable to the more powerful member nations), a few modifications must be made to this recommendation. First, process patents should be

applicable only to essential medications, as described in the first recommendation, to encourage research and development expenditure in other drug classes and in other technologies altogether. Secondly, to preserve some incentive for research in the field, certain restrictions should be placed against the second developer in commercializing its product in areas in which the discovering company holds a substantial proportion of the market.

In combining the above provisions, the result could be a highly efficient drug discovery and manufacturing process protected by patent, but flexible enough to adequately supply developing areas of the world.

Recommendation 3: Compulsory licensing: an obligation not an option.

The biggest problem with compulsory licensing, as described in the TRIPS agreement and its amendment, is that it is not written as a minimum standard that nations must implement into their domestic legislation to be TRIPS-compliant. Rather, it is written as an option that member nations have for implementation into their domestic legislation. As a result, only five jurisdictions that have the pharmaceutical capacity to be exporting countries under compulsory licensing have actually made progress on implementing these measures into their domestic legislation (18). If the Doha Declaration is considered to be an accurate reflection of the sentiments of nations, provisions on compulsory licensing must be incorporated into the TRIPS agreement as an obligation on member nations. At the very least, if separate classes of drugs are created, as outlined in the first recommendation, provisions on compulsory licensing for essential medications should be made a requirement in order to be TRIPS-compliant.

Article 31 of the TRIPS agreement specifies the conditions of use of compulsory licensing by member nations. It begins by stating "Where the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder" (6) in reference to compulsory licenses. The language of the article clearly leaves it possible for member nations to enact domestic intellectual property legislation without provisions for compulsory importing and yet still be compliant with the TRIPS agreement, the Doha Declaration and the Decision of August 30, 2003. The notion of compulsory licensing has very little value to public health if the only nations that adopt it are the ones that have no capacity to manufacture pharmaceutical products. Although it is true that parallel importing is also worded to be an option rather than an obligation, it does not pose as serious a problem because for a country to benefit from parallel importing, it must only amend its own domestic legislation to allow it; it is not dependent on the cooperation of other nations. On the other hand, a developing nation can only benefit from compulsory licensing if more developed nations enact it into their own legislation.

Detractors of this recommendation may argue that making these provisions obligatory, encroaches upon the sovereignty of a nation; but this must be looked at in the context of the TRIPS agreement as a whole. The agreement makes several provisions obligatory: patent protection must last for at least 20 years; process patenting is not permissible, public disclosure of the invention is obligatory, and so on. Making compulsory licensing obligatory in the context of a supra-national agreement that makes other provisions obligatory, particularly when it is consistent with an official declaration of the member nations, should elicit little political opposition on these grounds.

CONCLUSION

In conclusion, it must be reiterated that the lack of accessibility to essential medications by developing nations is a result of a number of factors; an unprecedented level of international collaboration and empathy will be required to make meaningful progress on this issue. This paper though, focuses on the factor that has been receiving the most attention: the WTO and its TRIPS agreement. The reason this facet of the problem is emphasized in this paper is three-fold:

- Of the many factors contributing to the current public health crisis, none are as simple to resolve, relatively speaking, than amending the TRIPS agreement.
- From my research, I have concluded that there are means that have yet to be addressed to balance the interests of commercial pharmaceutical enterprises with the human rights of patients in developing nations with.
- There is reason to be optimistic about the TRIPS agreement. The Doha Declaration, which affirms the commitment of WTO members to improving public health in developing nations is only five years old, this is a very short period of time in which to expect sweeping changes in international law. By lobbying our governments with creative yet pragmatic ideas, globally equitable healthcare can be a reality.

REFERENCES

1. Handelman H. The Challenge of Third World Development. Upper Saddle River: Prentice Hall; 2003.
2. Novak K. The WTO's Balancing Act. Journal of Clinical Investigations 112: 1269-1273; 2003.
3. Oh C. TRIPS and pharmaceuticals: A Case of Corporate Profits Over Public Health. Editorial. Third World Network
4. Striking a Balance: Patents and Access to Drugs and Health Care. Editorial. World Intellectual Property Organization
5. World Trade Organization Website. <http://www.wto.org>.

6. World Trade Organization. TRIPS Council. Trade-Related Aspects of Intellectual Property Rights (TRIPS); 1994. <http://www.wto.org/english/docs_e/legal_e/27-trips.pdf>.
7. Kohr M. The WTO, the Post Doha Agenda and the Future of the Trade System. Third World Network; 2002. <http://www.twnside.org.sg/title/mkadb.htm>.
8. International Intellectual Property Institute. Patent Protection and Access to HIV/AIDS Pharmaceuticals in Sub-Saharan Africa. World Intellectual Property Organization; 2000. <http://www.wipo.int/about-ip/en/studies/pdf/iipi_hiv.pdf>.
9. World Trade Organization. Doha Ministerial Declaration on TRIPS and Public Health; 2001. <http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.pdf>.
10. Brynen, Rex. Department of Political Science, McGill University. Personal interview; 23 Mar. 2005.
11. Correa CM. Implications of the Doha Declaration on the TRIPS Agreement and Public Health. World Health Organization; 2002.
12. World Trade Organization. TRIPS Council. Decision of 30 August 2003; 2003. <http://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm>.
13. Annan K. Interview. World Health Organization; 2001. <http://www.who.int/inf-pr-2001/en/pr2001-19.html>.
14. Chomsky N. Speech. Asian College of Journalism, Chennai. <http://www.greenmac.com/World_Events/aninterac.html>.
15. Rizvi M. TRIPS Will Push Health Care Beyond Poor. Editorial. Third World Network <http://www.twnside.org.sg/title/beyond-cn.htm>
16. United Nations. Universal Declaration on Human Rights; 1948. <http://www.un.org/Overview/rights.html>.
17. Bello W. Speech. XV International AIDS Conference, Bangkok; 2004. <http://www.alternatives.ca/article1363.html>.
18. Elliott R. Doha Para 6 Implementation: EU Proposal vs. Canadian Legislation. Online posting; 2004. <http://lists.essential.org/pipermail/ip-health/2004-November/007091.html>.
19. Amir A, Gillespie-White L. Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa? Journal of the American Medical Association 286: 1886-1892; 2001.
20. Consumer Project on Technology. <http://www.cptech.org>.
21. Boelaert M, Lynen L, Van Damme W, Colebunders R. Do Patents Prevent Access to Drugs for HIV in Developing Countries? Journal of the American Medical Association, Letters 287; 2002.
22. Goldberg RM. Fight AIDS With Reason not Rhetoric. The Wall Street Journal, 23 Apr. 2001.
23. The International Guidelines on HIV-AIDS and Human Rights; 2002. <http://www.icaso.org/docs/JFAP%20-%20Web.pdf>.
24. Weissman R. AIDS and Developing Countries: Democratizing Access to Essential Medicines. Foreign Policy in Focus; 1999.

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FEATURE REVIEW

The three princes of Serendip
Notes on a mysterious phenomenon

David R. Colman*

> "The seeds of great discoveries are constantly floating around us, but they only take root in minds well prepared to receive them."
>
> Joseph Henry, physicist and first director of The Smithsonian Institution

The word "serendipity" was entered into the lexicon by Horace Walpole in 1754. He had become intrigued with a Persian fairytale in which three princes of Serendip, (now Sri Lanka) traveled the world, "making discoveries, by accidents and sagacity, of things they were not in quest of..." Walpole proposed the new word, but then went on to give rather mundane examples of its meaning. It is only recently that serendipity has acquired its rather grand and mysterious significance.

The Oxford English Dictionary defines serendipity as "the faculty of making happy and unexpected discoveries by accident." Serendipity plays an important part in research of all kinds, but it operates only in a special environment; as Pasteur famously stated, "Chance favors the prepared mind." In research, what serendipity really means in practical terms is that scientists discover things in the course of their investigations that they were not looking for. And these new findings are often not the products of cold logic.

Sometimes, great discoveries are made because of a serendipitous situation or observation. One excellent example of a serendipitous observation which led to a great discovery occurred in 1922, when Alexander Fleming, suffering from a particularly juicy cold, happened to sneeze into a Petri dish full of bacteria. He absent-mindedly placed the dish on his cluttered desk. Some days later, as he was straightening his desk, he noticed to his great surprise that the bacteria in the dish had been destroyed. His curiosity was aroused, and following his nose (so to speak), he worked to isolate for the first time the "active principle" - lysozyme - the antibacterial protein found in tears and mucus. Convinced that more potent agents might exist, Fleming began searching for other environmental antibacterials, eventually coming up in 1928 with penicillin, for which he won the Nobel Prize in 1945. He shared the prize with Florey and Chain, who made the mass administration of the drug to humans practical. In his characteristic understated manner (he was after all the son of a Scottish farmer), Fleming commented,

> "Nature makes penicillin, I just found it; *one sometimes finds what one is not looking for."* (italics mine).

At the end of the 19th century and in another field, Wilhelm Roentgen, while working in his darkened lab with a Crooke's (cathode ray) tube, noticed out of the corner of his eye that several feet away, a piece of paper coated with barium cyanoplatinate was faintly glowing. He was puzzled, since the only conceivable source of energy in the room was the tube, which was not emitting visible light. When subsequently Roentgen found that sealed photographic plates in his desk had become fogged in the absence of a visible light source, he deduced that a novel form of radiation energy was being generated in the Crooke's tube. He termed the new radiation X-rays. Within a year after this discovery in 1895, X-rays were being applied in diagnostic medicine.

During World War I, a youngster named Cyril Astley Clarke was sent to the English countryside so as to be out of harm's way. It was there that he acquired what

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would be a lifelong fascination with butterflies. In fact, although he became a physician, he kept up his interest in inheritance of butterfly wing patterns, and made several original observations in this field. A friend of his suggested that he might also examine human blood groups from a genetic standpoint, and this serendipitous suggestion ultimately led Clarke to an understanding of blood group inheritance in humans, and to the development of an injectable antibody inhibitor (Rhogam) for Rh disease in newborns.

More recently, the multi-billion dollar biotechnology industry in great measure found its origins in a spontaneous, serendipitous detour:

> "It would sound reasonable if I were to say that the research work...began as a result of a grand design, with a vision of the goals in mind. Unfortunately, this would not be true. This work began the day I took a detour through Yellowstone National Park on my way to Seattle." (Thomas Brock)

On his first visit to Yellowstone, Brock became intrigued with the multi-coloured algae mats in the hot springs, and on a whim, took some samples back to analyze in his laboratory. In 1969, Brock and Freeze reported the discovery of *Thermus aquaticus*; this bacterium became one early source from which the heat-stable enzymes were purified - the key tools in recombinant DNA technologies.

And the pharmaceutical industry has benefited many times from serendipitous observations. Perhaps the best-known contemporary case is that of Viagra, which was originally tested as a treatment for angina. It was almost immediately found to be less effective than nitroglycerine for coronary artery dilatation, but then the patients in the first clinical trial reported an unusual, not at all undesirable and now well-known side effect. It is no wonder that the patients became depressed when the first clinical trials were brought to an end, and it was requested that the unused pills be returned to Pfizer. The company noted that never had so many unused clinical trial pills been reported as lost, misplaced, or accidentally flushed down the toilet...

But sometimes the serendipitous insight eludes the original experimenter, and alights instead on the reader of the experimental report, or (how embarrassing!) on a competitor. A well-reported published experiment may reveal to "prepared" readers a serendipitous discovery that might have been made at the time, but was missed by the original investigators. The fascinating experiments with sponge cells performed by H.V. Wilson in the early part of the 20th century fall in this category, and in a stunning way. Wilson set out to create chimeric sponges by dissociating cells of three sponge species, and placing them in the same dish to coalesce as combinatorial new species. To his extreme disappointment, the cells from each distinct species only sought each other out to aggregate with, and Wilson was unable to induce any chimeras to form. He wrote:

> *"1 shall here briefly record some experiments which gave only negative results...* These experiments were based on the assumption that if the dissociated cells of a species will recombine to form a regenerative mass and eventually a new sponge, the dissociated cells of two different species may be made to combine and thus form a composite mass bearing potentially the two sets of species-characteristics..." (italics mine).

It was only later that other scientists, most notably Ernest Everett Just, an African-American who was one of the great biologists of the last century, recognized the extraordinary implication of Wilson's "failure." Just, in reading Wilson's report, correctly concluded that sponge cell surfaces must display precise determinants that only allow aggregation between cells derived from the identical species. Hence, the cell surface is not "lifeless," as textbooks of Wilson's time stated, but rather,

> "The cell membrane stands not simply as a barrier of the cell against the outside world; it is also the medium of exchange between the cytoplasm and the environment. It is the first cell region to receive impressions from the outside world; through its delicacy of adjustment and fineness of reaction, it constitutes the first link in the chain of cytoplasmic reactions and sets the path for the orderly succession of events comprising the course in the differentiation of development." (E.E. Just, *The Biology of the Cell Surface*)

Competitors may be annoying recipients of the serendipitous insight. In 1887, Santiago Ramon y Cajal visited Dr. Luis Simarro Lacabra, a psychiatrist friend of his who had a histological laboratory in his cellar (medical students harken - his hobby was histology!). Cajal had been formulating the principles of the neuron doctrine, an extension of the cell theory of Schleiden and Schwann, but had not as yet found a way to verify his hypothesis that each neuron was a self-contained entity. Simarro took Cajal to his cellar laboratory, and showed him some brain slices prepared by the "black reaction" method of Camillo Golgi, an eminent scientist of the time who was an ardent proponent of the opposing reticular theory - that neurons are connected to each other via protoplasmic continuities that essentially make the brain a large syncytium. Cajal recalled that he was "thunderstruck" on his first look

through the microscope at the Golgi preparations, and he recognized in an instant that those slides would show the error in the reticularist's position, and demonstrate the validity of the neuron doctrine:

> "[Individual nerve cells appeared] coloured brownish black even to their finest branchlets, standing out with unsurpassable clarity upon a transparent yellow background. All was sharp as a sketch with Chinese ink... ideas boiled up and jostled each other in my mind..." (Cajal, "*Recuerdos di ma Vida*")

Golgi had had the data right in front of him, but was unable to interpret it correctly. Later Cajal would write of Golgi that he was "hermetically sealed" against new ideas. Golgi would not accept Cajal's conclusions, even though Cajal had used Golgi's own techniques to clearly prove Golgi wrong. The two shared the Nobel Prize in 1906, were on the same stage in Stockholm, but never uttered a word to each other.

Serendipity still plays a major role in discovery and invention. It is the manifestation of inspiration, and of being in the right place at the right time. To some, it has a certain magic about it that suggests predetermination or intervention by the supernatural, or as Shakespeare wrote:

> "There is a tide in the affairs of men, which, taken at the flood, leads on to fortune..." (Brutus to Cassius, in *Julius Caesar*)

In the end, though, probably the best way to sum up the phenomenon was most thoughtfully stated by Julius Comroe:

> "Serendipity is jumping into a haystack to search for a needle, and coming up with the farmer's daughter."

Dr. David R. Colman is the Director of the Montreal Neurological Institute. A native of New York City, Dr. Colman received his B.S. in Biology from New York University, and his Ph.D. in Neurosciences from the State University of New York, Health Sciences Center, Brooklyn, NY. He became an Assistance Professor of Cell Biology at NYU School of Medicine and joined the faculty of The Columbia College of Physicians and Surgeons as an Associate Professor of Cell Biology in 1987, where he received several prestigious awards, including an Irma T. Hirschl Career Development Award, the Harold and Golden Lamport Award, the Basmajian Award for Teaching and Research, as well as a Jacob K. Javits Neuroscience Award from the National Institute of Neurological Diseases and Stroke. He was subsequent the Annenberg Professor of Molecular Biology and Neuroscience at the Mont Sinai School of Medicine in New York City and the Vice-Chairman for Research in the Department of Neurology and the Scientific Director of The Corinne Goldsmith Dickinson Center for Multiple Sclerosis of The Mount Sinai School of Medicine. He began his tenure as Director of the MNI in September 2002. He holds the Penfield Chair in Neuroscience and a Tier I Canada Research Chair. Dr. Colman's research focuses on problems related to myelination and on nerve cell development with particular emphasis on synaptogenesis.

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FEATURE REVIEW

Understanding the human brain: A lifetime of dedicated pursuit
Interview with Dr. Brenda Milner

Chenjie Xia

As a pioneer in the field of neuropsychology, Dr. Brenda Milner has contributed to many important landmark discoveries in the study of memory and temporal lobes, the lateralization of hemispheric function in language, as well as the role of frontal lobes in problem-solving. She is a fellow of the Royal Society (London) and the Royal Society of Canada, and a Foreign Associate of the National Academy of Sciences (USA). She has been recognized with numerous prestigious awards throughout her career, the latest of which include the Donald O. Hebb Distinguished Contribution Award in 2001, the Neuroscience Award from the United States National Academy of Science in 2004 and the Gairdner Award in 2005. Dr. Milner received her undergraduate degree at the University of Cambridge in 1939 and completed her PhD under the supervision of Dr. Donald Hebb at McGill University in 1952. She joined the Montreal Neurological Institute in 1950 to work with Dr. Wilder Penfield. Dr. Milner is presently the Dorothy J. Killam Professor of Psychology at the Montreal Neurological Institute and the Department of Neurology & Neurosurgery of McGill University.

I spent an afternoon with Dr. Milner on May 12th, 2006, where she shared with me her thoughts on her work, her perspective on the past and future of cognitive neuroscience, as well as her advice for students beginning in research.

How did you first become interested in science, and more specifically psychology?

Both of my parents were musicians. My father was a music critic and pianist, and he met my mother when she started taking singing lessons from him. Unlike my parents, it was soon apparent that I had no talent for music. I did however have some interest in literature when I was young, which consoled them. In high school, I was always good at languages and my academic advisor suggested I go into humanities at Oxford. But as I loved mathematics and physics, I insisted on doing math despite everyone telling me I was foolish, and I managed to get a scholarship to study mathematics at Cambridge. That was in 1936, long before World War II.

When I got to Cambridge, I realized during my first year that I was never going to be a great mathematician. I believed, and I still believe, that you can always keep up with literature and languages on your own. Of course, it's different from doing a degree and taking classes, but you can do it if you are motivated enough. If you give up science however, you really give it up completely, because science is teamwork, which of course you really can't do by yourself. I suppose that was the reasoning behind what I ended up doing. Although I didn't stay in math, I still wanted to stay on that side, so to speak. So I thought maybe I'll do philosophy, since it is based on logic and I was a logical person. But then, everyone at Cambridge laughed at me and said, "Don't you have to earn your living? No one has ever earned a living in philosophy."

Nowadays, experimental psychology is grouped with natural sciences at Cambridge. However, before World War II, it was grouped with moral sciences, along with philosophy, logic and ethics. Thus, people around me suggested, "You shouldn't do philosophy, but have you thought about psychology?" And of course, I had not. Psychology had very little standing in England in those days, unlike in North America where it was more popular. I was given a big book to read over the summer and I decided to go into psychology. This was rather a

shock to my mother who had always hoped I would go into the arts side where she would then have been able to participate more in what I was doing. But she had reconciled herself to mathematics at Cambridge because it sounded pretty good. When I gave up mathematics to do psychology, I think she was really heartbroken.

So that was how I got into psychology. I knew I had to do very well, and I did do very well. I received a scholarship to stay on at Cambridge, which I suppose would be the equivalent of graduate studies in North America. Then, World War II broke out, and we were all put on to doing research for the Air Force. After my years on that scholarship, I worked in a radar research establishment, where I met my future husband Peter Milner, an electrical engineer. A couple of years later, in 1944, just as I was planning on going back to Cambridge to do more research, Peter was suddenly told that he was about to leave England with a group of physicists to go to Montreal, to help set up the beginning of Canadian atomic-energy research. When we arrived in Montreal, I had to get a job - I wouldn't have been happy not working. So I got my first job at the University of Montreal, where I taught animal behaviour and the experimental psychology of memory for several years.

How did you then end up working with Dr. Hebb at McGill? Did you have any particular reasons in choosing to do your PhD with him?

When we first came to Canada, the psychology department at McGill - and probably some other departments too - was pretty decrepit, since many people had left to do research for the war effort. In order to strengthen the department, McLeod, a distinguished experimental psychologist, was invited to act as chairman of the department. McLeod then recruited Donald Hebb who had previously spent two years at the Neuro[1] with Dr. Penfield and had published a few frontal-lobe cases before he went to study with Lashley in Orange Park, Florida.

I had realized by then that, in North America, you had to have a PhD to stay in academic life, which wasn't the case in England. It was at psychology seminars at McGill that I was attending where I first met Hebb. We were discussing the manuscript of his book The Organization of Behaviour and doing all the background reading. It was all very exciting. I was so impressed by Hebb that I decided to do my PhD with him. However, I had to persuade Hebb, because he wanted to be sure that I was serious, especially since I was a woman. In those days, women would often follow their husbands wherever they went and be lost to science. Nevertheless, I convinced him that I was quite serious about it.

How did you come about working with Dr. Penfield?

When Hebb agreed to come to McGill, one of the conditions he insisted on was that Penfield accept one graduate student of Hebb's to study his patients. This was at the beginning of temporal-lobe operations for epilepsy, and Penfield was pioneering this surgery at the Neuro. At the time, not much was known about the function of the temporal lobes.

As Hebb's graduate student, I had first worked on tactile concept formation in the congenitally blind. I had established some relations with the Montreal Association for the Blind, and had started some experiments that interested me. It was then that Hebb suddenly asked if I would like to go to the Neuro to study Penfield's patients for my PhD. I accepted, started working with Penfield's patients in 1950, and became absolutely fascinated. When I finished my PhD in 1953, I wanted to continue working with Dr. Penfield. Hebb told me I was a fool. The early 50's were a hard time financially for most people, and since I held a tenured teaching position at the University of Montreal, Hebb thought I shouldn't give up such a solid job. Moreover, since he didn't speak French, I'm sure he also liked having his ideas taught in French. He told me I was a fool, and that no psychologist could survive for long at the Neuro. I said I would still like to give it a try. Although he really thought I was crazy, he still offered to support me for one year from his grants. So I left the University of Montreal and started working in the psychology department at McGill.

In the course of that year, Penfield and I saw two patients with severe memory impairment after their surgery. Before these two patients, I think Dr. Penfield genuinely thought he could be his own psychologist. He encouraged people to come and study his patients, but he thought psychology was just common sense and that he had plenty of it, which was true. When this memory impairment presented itself, things changed. You have to realize that temporal-lobe operations for epilepsy are elective. It's not the same as someone having a large brain tumour or vascular lesion, where you are trying to save their life. In that case, if the patients become paralyzed, lose their speech or memory, they are at least alive. It is different with epilepsy, and it really disastrous if your patients suffer serious memory loss. Penfield said to me, "You have to come to the Neuro, we need you!" I never thought the great Dr. Penfield would say "we need you." But he found me a little office close to the neurosurgical offices. And so, I

[1] At McGill, The Montreal Neurological Institute is commonly referred to as "the Neuro."

started working at the Neuro and have stayed there ever since.

Was HM one of these two patients with memory impairment?

No, not at all. This is something I have to repeat continually, because everyone seems to get it wrong. The first patients I saw with this memory problem were PB and FC, both of whom taught us a great deal.

In the early days when Penfield was beginning to operate on the temporal lobes for epilepsy, he was very cautious. In those days, you didn't know before going into the surgery what you were going to find. All you had was the plain X-ray films of the skull and a pneumoencephalogram where you would only see the size and shape of the ventricles. We also relied on the beginnings of EEG developed by Dr. Herbert Jasper, but EEG at that time were also very primitive. Before I arrived at the Neuro, Dr Penfield was confining the removal to the anterior temporal neocortex, and of course always to one side only. But as time went on, he realized that this neocortical excision was rarely controlling the epilepsy. The reason he had not touched the hippocampus up until that point was not because he had an intuition that it had something to do with memory, but rather because he thought that this huge, beautiful structure must be important, and why should you take it out if you don't have to. But as people returned from the surgery with their epilepsy still uncontrolled, he realized that he had to be prepared to take out the amygdala, part of the hippocampus, and some surrounding tissue from the medial temporal region. That was the state of affairs when I began working on my thesis.

PB was a civil engineer from the United States. He had had a neocortical removal from the left temporal-lobe in 1941, before I arrived at the Neuro. He came back about 10 years later still having seizures. So Dr. Penfield completed the temporal lobectomy, taking out the medial structures during the second surgery. The lateral structures had been removed during the first surgery. I tested PB extensively before and after the second surgery, as I was doing with all of Penfield's patients. I could show that, before surgery, this man's intelligence, as measured by the IQ test, was well above average, and his immediate memory span, his old memory and knowledge were all normal. But from the surgery onward, he was not remembering anything of everyday life. He would say to us, sarcastically, "What have you people done to my memory?" It was our first encounter with this peculiar memory impairment. Dr. Penfield, Dr. Jasper and I wondered what was going on. Penfield was of course very worried. Jasper, on the other hand, tried to reassure us, and said that there is probably a peculiarity about this one patient that we didn't know about. A month later, we had another patient, FC, with the same result. FC was a glove-cutter and he had a one-stage left temporal lobectomy (including part of the hippocampus) and developed the same syndrome. At that point, Penfield and I speculated that this was the effect of a bilateral lesion, and that possibly unknown to us or misdiagnosed by us, there was more damage or atrophy in the hippocampal region of the opposite hemisphere, the right non-operated side. Thus, when Penfield removed the left hippocampus, he was effectively giving the patient a bilateral lesion. The emphasis on the hippocampus came from the fact that we only saw the impairment after the second procedure in PB, which involved only the medial structures of the left temporal-lobe.

We presented the data and this hypothesis at the American Neurological Association meeting in Chicago in 1954. After the meeting, Dr. Penfield got a phone call from a surgeon in Hartford, Connecticut, Dr. William Scoville. He said to Penfield that he had read our abstract with great interest and that he had seen the same result in a patient of his own after his operation. To put this in context, we have to go back in time into the bad old days of frontal lobotomies for schizophrenia. Scoville had carried out some of these operations and was not happy with the results. He had wondered if, in schizophrenics, it would help to do a bilateral medial temporal removal, because everybody was talking a great deal in those days about the connections between the medial temporal regions and the orbito-frontal cortex. He was a very good surgeon and he had developed an operation going in from the front and removing, depending on the patient, different parts and different degrees of the medial structures of both temporal lobes. This operation was different from Penfield's both in being bilateral and only medial, sparing the neocortex. Dr. Penfield used to say that it really fitted well with the Montreal operation almost as a planned experiment, since ours was a unilateral temporal lobectomy, and Scoville's operation was a bilateral medial excision and the common feature was the involvement of the medial structures. Scoville did this operation in different hospitals on patients with very severe schizophrenia, but he had not really followed them up. I studied some of his patients afterwards and found the same memory impairment in them, as far as it could be tested.

HM was not schizophrenic. He was a normal young man who had had very bad seizures from quite an early age, the etiology of which is not clear. It did not manifest itself as temporal-lobe epilepsy. He had many major convulsions and some absence attacks. He was on maximal doses of the anticonvulsant medications

available at the time. He was potentially of above average intelligence (as shown by postoperative testing), but was so obtunded from all these seizures that it took him many years to finish high school and he could not successfully hold a job afterwards. He was a desperate young man and had consulted Dr. Scoville for several years, seeking relief from his epilepsy. Although HM's epilepsy did not have a temporal-lobe origin, Scoville wondered if his temporal lobe surgery would be helpful, as he had become increasingly aware of the epileptogenic properties of the hippocampal region. This possibility was extensively discussed with HM, and eventually the operation was carried out. Actually, as far as the epilepsy was concerned, Scoville's judgement was right. Since the operation, HM had on average one big attack a year and a few small ones, and he is on considerably reduced medication. As mentioned earlier, Scoville had not followed up the schizophrenic patients, and suddenly this terrible memory impairment was obvious to him for the first time. Actually, Scoville published a paper in 1954, in the Journal of Neurosurgery, called "The Limbic Lobe in Man," in which he commented on this patient who "has lost his memory, but preserved the niceties of ward life", in that he was polite and knew how to behave, but couldn't learn his way to the bathroom and couldn't remember any of the hospital staff, except Scoville, whom he had known for many years.

When Scoville encountered our report, he called Dr. Penfield and suggested that we go and study his patients if we liked. So I started this really exciting period where I would go down by train to Hartford, work with HM for a few days and then come back to Montreal and think about what I had found. That was the beginning of the story of HM. He was not a Montreal patient, and Penfield never performed a bilateral medial temporal operation.

However, I should go back to PB for a moment. Penfield and I had speculated that there would be damage on the other side to account for the postoperative memory impairment. Years later, PB died of a pulmonary embolism. Penfield had maintained good relations with PB's wife and family and was able to carry out an autopsy on his brain, which confirmed that there was indeed atrophy of the right hippocampus, on the unoperated side, thus validating the hypothesis we had come up with to account for the memory loss.

Do you remember the moment when the idea of multi-system memory came to you? Was it an "aha" moment or did you have to think it through very carefully?

It was very much of an "aha" moment. I had met HM and had done all sorts of single-trial tests that demonstrated the severity of his memory impairment. Then the question arose as to whether he could learn something new over multiple trials. So I went to the Introductory Psychology Lab of the Psychology Department, picked up a couple of tasks I could carry, and took the night-train for Hartford with my equipment. I suppose I chose good tasks: one was a maze task where you learn the path by trial and error; the other was a mirror-drawing task. Whereas HM made no progress with the maze, he showed good learning with the drawing task. It was a sensorimotor task, in which you are presented with a double-bordered five-pointed star and your goal is to trace a path that keeps within the two borders. The task would be extremely easy but for the fact that you only see the star and your hand as reflected through a mirror. This is difficult for anyone at the start, but with practice we improve, and so did HM. After three days of practice, his performance was perfect. He had really shown beautiful learning, although he had absolutely no awareness that he had ever done the task before. I then realized that this kind of learning is dependent on another system of the brain and I speculated that this applied to all kinds of motor learning. It was a very important breakthrough. To see that HM had learned the task perfectly but with absolutely no awareness that he had done it before was an amazing dissociation. If you want to know what was an exciting moment of my life, that was one.

How did you then make the jump to study interhemispheric specialization?

The interhemispheric specialization was not a jump. I started with interhemispheric specialization, not with memory. When I went to the Neuro to study Penfield's patients, I was trying to study the functions of the temporal lobes. But of course, since only one side was removed during the temporal lobectomy, in most patients (except PB and FC), there was a remaining functional temporal lobe. I compared groups of patients, the left (dominant) hemisphere group with the right hemisphere group. In those days, there was a strong neurological bias to speak of the dominant hemisphere, instead of language dominant as we say now. All good things were attributed to the left hemisphere. A very famous neurologist wrote about the dominant hemisphere and language with a very contemptuous dismissal of the other side.

I thought this was ridiculous, one of the reasons being that I had always been impressed by experimental work in psychology with monkeys. Monkey experiments can guide your work on the right hemisphere, but not the left hemisphere because monkeys can't talk. I was very much guided by the work with monkeys, which was beginning to show that there was an area in the temporal

lobe which seemed to be involved in complex visual memory. I remember Dr. Penfield looking at me in amazement and saying, "The temporal lobe is so far away from the visual cortex, why are you looking for visual effects there?" In those days, we didn't know about the ventral visual stream. I showed in my thesis that patients with right-temporal lesions (but not those with left) had difficulties with visual perception and memory, and that's essentially where my idea of complementary specialization of the two sides of the brain came from. Later on, I met Roger Sperry, from Caltech, who was studying patients on the west coast who had undergone cerebral commissurotomy, also for the relief of epilepsy. He invited me to visit him if I were interested in knowing what was happening on the right side of the falx. I accepted his invitation and studied various aspects of hemispheric specialization on his patients. So my work in this area pre-dated my work in memory and I would say that the notion of complementary specialization of the two sides of the human brain was a guiding theme throughout my career.

What role did your work on frontal lobes play in your career?

The frontal lobe was a funny story. When I first arrived at the Neuro, the frontal lobes were being debunked and were wildly unfashionable. Many extravagant claims had been made about them in the past, often based on bad data such as those from patients with huge tumours, or from lobotomies performed on severely schizophrenic patients. These studies were very tricky to interpret because they introduced many confounding factors.

We had far fewer patients with frontal lobe epilepsy than with temporal-lobe epilepsy, so we gathered the data slowly. I was following all the work going on in Wisconsin on bilateral frontal lesions in monkeys and was particularly interested by this difficulty the monkeys had with reversal learning, that is, the difficulty with learning one thing and then reversing to learn the opposite. David Grant was a very fine experimental psychologist working at the University of Wisconsin. He and one of his students invented the Wisconsin Card Sorting Task which was inspired by work with monkeys. I wrote to David Grant and told him I was interested in using this task with my frontal-lobe patients. He wrote back very enthusiastically and sent me the test materials. I collected very beautiful results demonstrating reversal-learning impairments in patients with dorsolateral frontal-lobe lesions, which were published in 1963.

During the two years Donald Hebb had worked with Penfield, the patients they saw had mainly been post-traumatic frontal-lobe cases. There was one famous patient, KM, who was a workman in Nova Scotia. He sustained a very severe injury at work that destroyed on-third of both frontal lobes, similarly to Phineas Gage, and he developed post-traumatic epilepsy. He was sent to Penfield, and a bilateral frontal-lobe operation, which essentially consisted of cleaning up the lesion, was performed. Hebb studied KM pre- and post-operatively with a few basic intelligence tests and found no loss with the tests that were given. Hebb and Penfield both published very famous papers about the frontal lobes at this point, and Hebb became very skeptical of the importance of the frontal lobes for intelligent behaviour in the adult. He thought that maybe when you are growing up, you need the frontal lobes to develop your intelligence and skills, but once a certain level is reached, you are just running off your skills routinely - the frontal lobes playing only a minor role. Several other people, including the neurologist, Ritchie Russell in England, had adopted this view as well.

Years later, after I had published on card sorting in frontal patients, I got a chance to see this same patient, KM, on follow-up. He was no longer having seizures and I replicated all Hebb's findings on standard intelligence tests, but he failed completely on the Wisconsin Card Sorting Task. He showed the deficits that I predicted he would have, whereas he was fine on some of the memory tests that HM would fail. It was all very clear. But until the end of his days, Hebb could never quite assimilate this. In his capacity as my former thesis advisor, Hebb was often asked to write letters of recommendation for me for various reasons. When he wrote to me to bring him up to date on what I was doing, he would sometimes say, "Brenda, I think I know your temporal-lobe work very well. And I think you found out something about the frontal lobes, but I'm blessed if I can remember what it was!" I used to get cross about that; now it just makes me laugh.

So that was the beginning of the frontal-lobe story. Now, of course, the frontal lobes are everybody's love and I'm back in the temporal lobes.

Out of all your projects, which was your favourite part?

That's awfully difficult to say. Of course, the amnesia part has had the most impact. That's what I am sort of famous for, gotten awards for, and talk about more and more now because people like to hear the history.

I probably got the most kick out of the frontal patients. I like working with frontal-lobe patients very much. They do such unexpected things! I still remember this man with whom we were doing card sorting, the first category being colour, then shape, then number and so on. He was going on and on, failing the first category. And in my simple-minded way, I wondered whether he

was simply color-blind! But of course, he wasn't. It was just amazing to see someone whom you knew to be perfectly intelligent behave in such a way. This inability to regulate their behaviour by external cues is absolutely weird. I find it difficult to empathize with frontal-patients in this situation. Temporal-lobe patients forget - we all know what it's like to forget; it's a terrible handicap, but it's not actually a very interesting state of mind. It's much harder to understand what it is like being a frontal-lobe patient, so I am much more intrigued by it. They have lightened my life with the totally unexpected things they do.

How do you usually come up with a research idea?

The thing about me is that I am not a theoretician. I don't mean that I don't know other people's theories, I do read about others' work. But I'm not someone who comes up with great cognitive questions and then sees how I could answer them. I am extremely empirically driven. My quality is that I am a very good observer. I would note a funny little quirk in a patient and would think, "Well, that's interesting! Why did the patient do that?" and then try to Figure how I could find out more about it and test it in a more scientific way.

I will give a small example. When I started working with left frontal-lobe patients, they were fine on their global intelligence, they weren't aphasic, and they were cooperative. But remarkably, they were lacking in spontaneous speech. I remember particularly this one young woman because she was very pleasant. She had a good IQ and including good verbal intelligence, but she was just not saying or writing very much. She even complained that her friends had stopped visiting her because, as she wasn't saying very much, they thought she didn't want to see them. I thought this was very interesting and that maybe frontal-lobe patients just weren't fluent, although their word-knowledge was fine; there is an important difference between word knowledge and word use. With that idea in mind, I started testing them with standard fluency measures. I was able to show clearly that these left-frontal patients had a deficit in word fluency. It is classic now; but back then, it was stimulated by observing that this cooperative and friendly woman was saying very little, despite having good verbal intelligence. It's something that strikes you and then makes you want to explore it further.

Throughout the early years when you worked with Dr. Hebb and then Dr. Penfield, how would you compare the field of experimental psychology back then to now?

As a discipline, I don't think experimental psychology was that different back then. There were scientific ways of studying behaviour, and that was what psychology was about. Now, we have many more resources, especially in the last 15 years. We now have all this new technology such as neuroimaging. Structural MR was an enormous advance - those of us who are interested in looking at anatomical and physiological correlates of behaviour are able to do so now.

When you ask about psychology, you have to look at the impact of Hebb. Experimental psychology was a very well established discipline, with methods on how to analyze data, do statistics, and how to design experiments. I would say that was the same back then as it is now. But the idea of looking for the neural correlates of behaviour, the idea of putting those things together, what they now call cognitive neuroscience and what we called physiological psychology, was novel and was criticized by both sides. When Hebb wrote his book, he was criticized by some of the most senior and distinguished experimental psychologists of the day. They believed that we can do very scientific analyses of behaviour and make our own logical constructs to explain behaviour, but that when you start linking this to the brain, it's very premature. When you come to the side of medical people and physiologists, they were equally critical. They would say to Hebb that what he was doing was not physiology, but rather "physiologizing." By insisting on putting these two fields together, Hebb was a real innovator.

You were one of the first to bring together the fields of neurobiology and experimental psychology. You were also one of the first to integrate the clinical side into all this by studying lesion patients. What convinced you this was the right approach?

Well, I just loved it. Also, I was very lucky in that the psychology department at Cambridge, where I had studied before the war, always had a tradition that was very biological. We had to read a lot about the brain for our exams and so on. For example, if I had gone to London University, which also had a very good psychology department, I would have had an entirely quantitative psychology: intelligence; factor analysis: mathematical psychology. It would have been measurement, measurement, and measurement, with nothing about the brain. I think this is partly why Hebb chose me as his graduate student. I remember for our final exam at Cambridge, there was one exam of three-hour essay writing where we had a choice of six topics. I wrote on cortical localization of function, on sensory and motor systems, and a bit about language, because that was really all that was known. But it shows what we were trying to learn about at Cambridge in 1939. I think perhaps with this background, it was easier for me to assimilate Hebb's integrative approach than for some of the North American graduate students, where

psychology tended to be less biologically based.

I was considered very foolish to continue doing what I was doing. I'll make it a little bit of a caricature. It was supposed that, either you would take twenty rats through a learning study where you could do something physiological with the rats, or you would take twenty undergraduate students and perform some kind of psychology experiment on them. I, on the other hand, was taking experiments of nature. I couldn't just say, "Let's take these people's temporal lobe out." I had to take the patients as they came; I had to take them with whatever associated difficulties they had, their different degrees of epilepsy, and try to make sense of what was coming my way. People thought this was a foolish way to go, that it was better science to study the rats or the healthy undergraduate students than to study patients. Then, later, people said, "Well, you were so lucky." But I think I was just fascinated.

In a lot of your work, you were interested in lesion location linked with function. More and more work is now put into grouping different functions together into pathways and systems. If you had fifty more years, how would you take the work you have done up until now and integrate it into a system?

This is a very tricky thing, because I think it brings one back to the difference between functional brain imaging and the lesion method. You need both. With the lesion approach, you have someone who has had a permanent effect of this specific lesion, like HM, and you can know that the damaged structures were in some way critical to this kind of ability. With brain imaging, you can say that when this person is doing some kind of task, these areas light up. But you don't know which of these areas are really critical to the performance of the task and which are simply incidental. So you really need both approaches.

But of course, a much harder question is not that. The much harder challenge, which I have no answer to, is to put the molecular and the systems together. I certainly don't know how that is going to be worked out. It's not easy and it's not anything I'm going to contribute to, because I don't have the knowledge. It's not just because I'm 87, I could be 67 and it would be the same. I know a lot of younger people who are struggling with the same problem.

Do you think that the way we train very specialized researchers nowadays perpetuates the gap between the systems and the molecular?

Yes, I think it's a real problem. For example, when one attends a lecture on molecular topics which requires the knowledge that gene G58 does this or that, it's a whole new vocabulary that most behavioural scientists just don't have. But I think it's a question of different temperaments as well. Some people feel very secure doing molecular work. I can remember the late Patricia Goldman saying that psychology was difficult, even though she was a distinguished psychologist. She retreated into molecular work because she found it easier. I think you have to look at the different kinds of brain and what comes easier to each of us. Certainly, one has to give beginning students in neuroscience more of a broad basis. But when the chips are down, you'll still find some people who like doing the molecular kind of research and some people who like doing the systems kind of research. There are going to be great people who can bridge the two, but it's not going to happen so quickly. But then again, I don't have a crystal ball, I'm not a prophet.

What do you think were the major changes that have occurred in the MNI over the past fifty years?

I think we have to say changes within the context of remarkable continuity. What is very special about the MNI is that Penfield's vision has been preserved in his successors, this wonderful bringing-together of people from so many cultures and backgrounds from all over the world, putting together the different clinical and scientific questions in the same house, same building; this remarkable family feeling is still here at the Neuro even though it has grown so big.

The big change was of course the bringing-in of the molecular. There was no molecular science at the Neuro in the old days. Even when people began to realize that the molecular was important, it was thought that that would be done at the Montreal General Hospital. The predecessor to the present director was actually brought in with the mandate to encourage the development of this whole side of neuroscience. Now of course, we have many molecular groups working at the Neuro, but you still have the challenge of getting the molecular and the behavioural groups talking to one another. Most of the scientists are still very much in one camp or the other.

What would you like to see in the next fifty years for behavioural neurosciences?

I really don't know, although I know which way it is going and it's not the way I would like to go. People now are looking at emotions, adolescence and social interactions, which one always felt were perhaps not very amenable to studying in the individual brain. This branch of psychology has never appealed to me personally, but I do think the field is moving that way with what I call these big fishing trips. They are beginning to think that they can ask questions or tackle issues that previous scientists thought not amenable to

the neuroscience approach.

How do you work with your students in coming up with a research project?

I've never given a student a specific project. I tell them what we are working on, I throw ideas onto them. Sometimes, they come back with things that don't quite work, but along the way, they find out what they are interested in.

For example, I wouldn't say, "I have this project written up in my grant for the CIHR and I'd like you to do the experiments." I would never do that. There's a real difference between being a research assistant and being a graduate student. When you've had your work and your projects considered worthy of funding by an agency and you've said to the granting agency that you are going to do these experiments, you hire a research assistant to help you do the experiments. That is a job. Graduate students are supposed to be learning what they are interested in. Obviously, if I am working in the field of learning and memory, and somebody comes along wanting to work on schizophrenia or emotions or something else, I tell them that I'm not the right person to be their supervisor. But if they are interested in the general area I'm working in, I expose them to everything that we are concerned in and the things we are tackling. Then, I ask them to do quite a bit of reading. They may come back with an idea that is not very well formulated and I can help them formulate it. But I am not going to tell them what experiments they should do. I know there are many supervisors who treat their graduate students as research assistants. I think this is unethical.

What qualities do you look for in your graduate students? What kind of skills do you encourage them to develop?

They have to have a lot of curiosity. Curiosity is what keeps me going at the age of 87. And there are a lot of other things. They must not have any illusions about science. They must not have any romantic notion that they are going to make a great discovery once a month or even once a year. There's an awful lot of routine in any job. You have to be willing to take a lot of measurements. You know that in molecular fields, you are doing a lot of boring bench work, but in this field too, you are doing a lot of routine work. For example, if you want to study spatial abilities or tactile modalities of patients with parietal lesions, you have to know about their thresholds for two-point discrimination. You have to take all kinds of very careful measurements of basic capacities before you can start speculating about higher functions. This can be very boring if you don't have the right attitude. I think people have to be very patient. They also have to be ready to go into the lab. Hebb perhaps went to extremes that way. He really didn't encourage people to do all that much studying. He wanted them to be in the lab as soon as possible.

Another quality I look for in a graduate student is the ability to write. However, I think that you can learn to write and I've certainly taught people to write. I once had a student, a good student, who had always fancied herself as a literary person. She had taken many literary courses and wrote short stories. That kind of writing is fine, but it's not scientific writing. Not being able to write clearly is a big handicap, and I think writing clearly and thinking clearly are closely linked.

For students learning how to write scientifically, what advice would you give them?

Of course, you have to have someone who is willing to teach you and work with you. I have seen very good scientists who just don't care. I've read theses in which the experiments are good, but the writing just made my hair stand on end. The supervisor just didn't think it important, but it really is. I actually got that from Hebb - he really valued good writing. The really big thing is to anticipate your readers' needs. I remember working on my thesis. I prided myself on my writing and I remember giving Hebb the historical introduction to my thesis which I was quite proud of. He gave it back to me and said, "Can't understand it! Can't follow it!" I was so insulted; I didn't look at this thesis for about a month. And then I thought, "I'll show him!" I started realizing what the problem was. It was all there, but you have to anticipate your readers' needs. You have to tell them something in advance if they'll need it in the next paragraph. You mustn't tell them something at the end that they needed earlier on. You know these things, because it's your work and it's all in your head, but the poor reader doesn't have your head. This is absolutely a huge thing that people have to learn and then, it becomes second nature. After showing the second draft to Hebb, he said, "This is excellent, this would make a good article in the Psychological Bulletin," and it actually ended up being my first publication.

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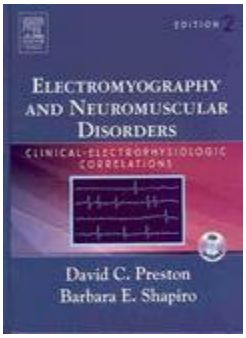
BOOK REVIEW



Electromyography and Neuromuscular Disorders: Clinical Electrophysiologic Correlations, 2nd edition, by David C. Preston and Barbara Shapiro

Elsevier, 2005, 704 pages.
ISBN-13: 978-0-7506-7492-8
$227.00 CAD

Seldom in the realm of medical texts does one encounter a truly readable and accessible textbook that doesn't sacrifice content for clarity. Such a truly rare feat is accomplished in the most recent incarnation of Electromyography and Neuromuscular Disorders: Clinical Electrophysiologic Correlations by Preston and Shapiro. Although it has a relatively small readership base, limited to neurologists with an interest in electrophysiology, physiatrists or very enthusiastic residents and medical students, this book is frequently lauded and praised by all those who read it. This most recent edition includes updated content, but the most notable improvement is the addition of two companion compact discs. These CDs provide excellent quality audiovisual aids that compliment the content and help illustrate key electromyographical findings.

The book is divided into several sections. Sections one through five focus mainly on explaining fundamental principles of electrodiagnostic tests such as electromyography (EMG) and nerve conduction studies (NCS). In addition to comprehensive explanations about performing and interpreting basic studies, there are also chapters dedicated to other more specialized tests such as repetitive nerve stimulation and the blink reflex. Specific sections are also completely dedicated to important, but frequently overlooked topics such as sources of technical error, anatomical variants and basic statistics for electrodiagnostic studies. These chapters are particularly helpful as they demystify topics that are often not covered in adequate breadth and depth in other textbooks.

Section six focuses extensively on clinical-electrophysiologic correlations. This section includes chapters on all of the common mononeuropathies, such as median, ulnar and peroneal. Each chapter provides a detailed review of the relevant anatomy, common clinical presentations, common etiologies, a differential diagnosis, and an approach to the electrophysiologic evaluation. Diagrams and figures illustrating key findings or concepts are interspersed with the text and contribute significantly to clarifying complex concepts. Each chapter also includes several cases that enable the reader to work through actual clinical scenarios and apply the concepts learned in the chapter. These cases are instrumental in reinforcing key concepts and helping the reader consolidate their knowledge. Each of these chapters close with a summary and a Socratic style discussion with responses to commonly asked questions.

Section six also includes chapters on polyneuropathy, amyotrophic lateral sclerosis and other motor neuron diseases, radiculopathies, plexopathies, and sciatic neuropathy. Each of these chapters implements the same formula and meticulous approach employed in the earlier chapters, and focuses in detail how to differentiate between these different conditions on the basis of electrophysiologic testing. Numerous cases also help to illustrate important concepts on how to avoid common diagnostic pitfalls.

In addition to the ample content, this book also includes two companion CD-ROMs that nicely compliment the explanations in the text. The CDs run on both PC and Mac and provide a comprehensive library of common and rare EMG sounds, waveforms and findings. Each video clip is accompanied by a concise, yet complete explanation of what you are observing and the clinical significance of these findings. The CDs even include a quiz that the viewer can use to test their skills.

Overall, Electromyography and Neuromuscular Disorders: Clinical Electrophysiologic Correlations, 2nd edition is a superb book. Its two authors succeed in achieving the rare balance of writing a thorough and comprehensive text while still maintaining an accessible, easy to read style. This book would make a wonderful addition to the library of any neurologist, physiatrist or other physician with an interest in electromyography.

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Commentary – longer than letters but generally consisting of fewer than 700 words, on a topic of general interest. Unsolicited Commentaries are welcome but authors should contact the Editor-in-Chief to discuss the topic before submitting.

Focus Article – solicited articles on a subject chosen in advance by the Editorial Board.

Book Review – comments on a book of general interest. Recently published books are preferred but older books still considered to have wide appeal are appropriate. Unsolicited book reviews are welcome but potential authors should contact the Editor-in-Chief to discuss the book before submitting.

Artwork - originals or digital can be submitted

Peer reviewed (First author must be a student)

Original Article – full-length article reporting the results of an original research project. In addition to presenting the project and its findings, the project's rationale and the significance of its findings must be clearly explained.

Case Report – report and discussion of a clinical case that illustrates some important teaching points. Authors must clearly explain the significance of the chosen case and the teaching points illustrated by it.

Review Article – overview of the understanding and outstanding questions in a particular field of research. Review articles that explore a specific hypothesis and/or combine information from different areas of research to advance an original idea are especially encouraged, as opposed to review articles that simply enumerate past findings.

Crossroads – similar in style to review articles. "Crossroads" articles should explore the relationship between medicine and the humanities (visual arts, literature, history, philosophy, etc.).

ORGANIZATION

For all peer reviewed articles, each required component should begin on a new page and appear sequentially, as follows. Original articles: title page, abstract, introduction, methods, results, discussion, acknowledgements, references, tables, and illustrations. Case report: title page, introduction, the case, discussion, acknowledgments, references, tables, and illustrations. Review and "Crossroads" articles: title page, introduction, body of text, conclusion, acknowledgments, references, tables, and illustrations.

Tables

Tables must be submitted typewritten in the order corresponding to their first citation in the text and accompanied by brief titles. All non-standard abbreviations must appear below the table with an accompanying definition.

Illustrations

Figures and legends should contain sufficient information such that each figure is intelligible without reference to the text. Figures must be printed on high-quality paper. Photographs should be glossy in black and white. Authors may submit color prints but, if published, must bear the extra printing costs. Each figure legend (with figure title and corresponding figure number) should be submitted on a separate page.

REFERENCES

Reference citations should appear in numerical order in parentheses throughout the text and be listed in their order of appearance. References should be formatted according to the examples below.

Journal articles

1. Bunny B, Coyote WE, Le Pew P, et al. Impact trauma Caused by Descending GPI Anchors. McGill Journal of Medicine 2003; 7: 1-2.

Books

2. Bunny B, Coyote WE, Le Pew P. Subdural Hematomas. In: Jones J, ed. Head Injuries. New York: Acme Publishers; 1994: 249-260.

Internet

3. Bunny B. Computer-induced psychosis. Society for Cartoon-Computer Interactions. http://www.SCarComI.com/psychosis.html. 1999.

EDITORIAL REVIEW PROCESS

All submissions of "peer reviewed articles" undergo a formal and anonymous evaluation process conducted by the *MJM* Editorial Board, comprised of trained students with diverse areas of expertise. This peer review process is performed in two stages. During the first stage, the manuscript is evaluated individually by each member of the Editorial Board. For submissions requiring revision, a detailed manuscript evaluation summary is returned to the author with suggestions for improvement. Manuscripts of high caliber proceed to the second stage, in which a review is performed by a McGill medical faculty member whose field of expertise correlates with the subject matter of the paper. Comments from the faculty expert are synthesized with the evaluations of the Editor-in-Chief, Executive and Senior editors, and members of the Editorial Board to achieve a decision to accept, defer, or reject the paper for publication. In all cases, a detailed manuscript evaluation summary is returned to the author along with any suggestions for revision.

After appropriate revision, the manuscript text must be resubmitted on diskette and a copyright transfer agreement signed. Prior to publication, authors will be required to review edited proofs without delay.

SUBMISSION OF MANUSCRIPTS

Manuscripts must be submitted by e-mail in MS Word format to *mjm.med@mcgill.ca*. You may contact the McGill Journal of Medicine through the Faculty of Medicine, McGill University, 6th floor 3655 Promenade Sir William Osler, Montreal, Quebec, Canada H3G 1Y6. The *MJM* Editorial Division may also be contacted by telephone at (514) 398-6987, or by e-mail at *mjm.med@mcgill.ca*.

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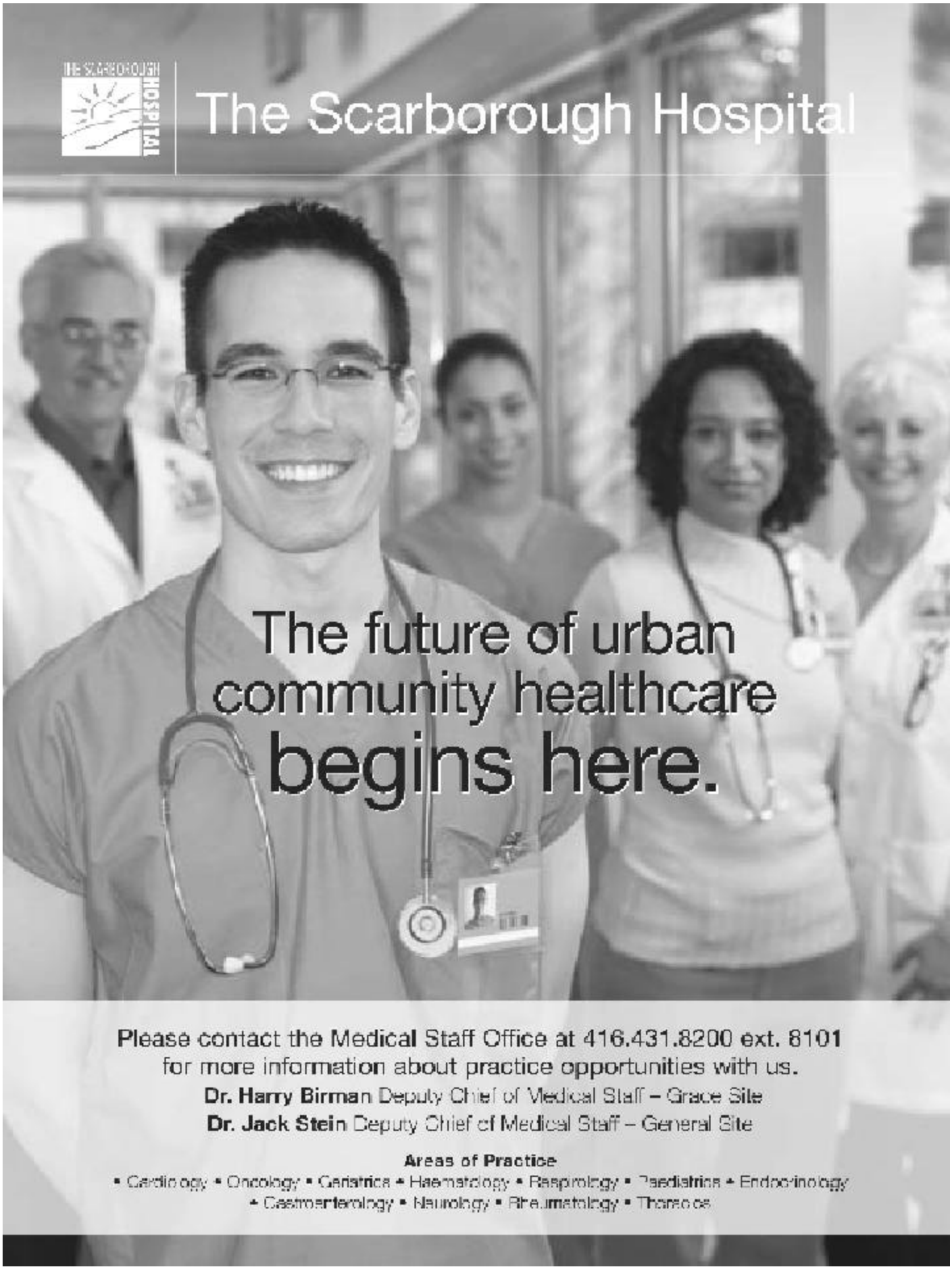

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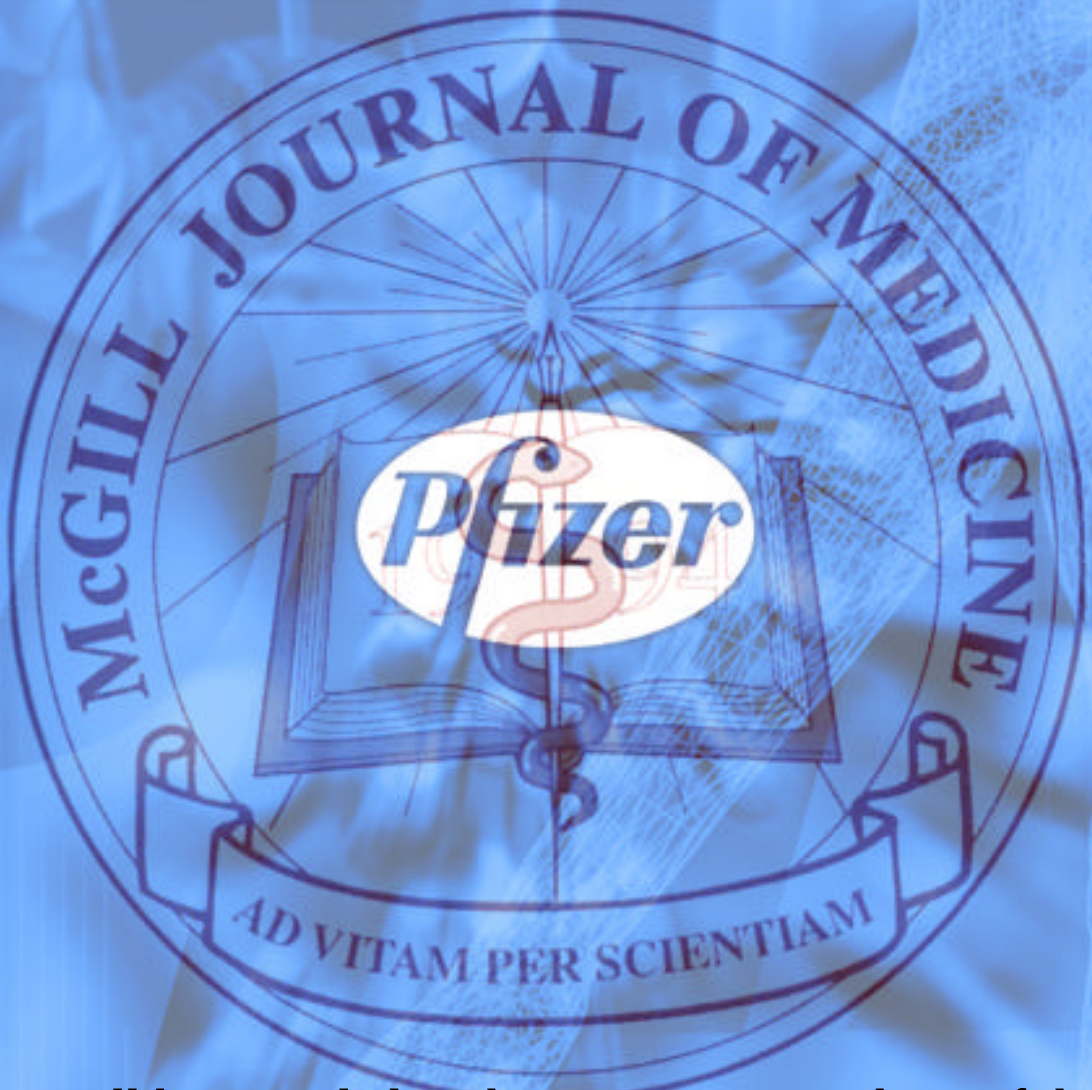

Prizes will be awarded to the STUDENT authors of the top original research articles submitted for publication in the MJM issues 9.1 and 9.2

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